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VOLUME 17 NUMBER 6

ARCHIVES OF SURGERY

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DECEMBER, 1928

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second-Class Matter, July 10, 1925, at the Postoffice at Chicago, Illinois, Under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of Oct. 3, 1917, authorized July 29, 1920.

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ARCHIVES OF SURGERY

VOLUME 17 DECEMBER, 1928 NUMBER 6

PANCREATIC FUNCTION TESTS

WITH SPECIAL REFERENCE TO THE QUANTITATIVE DETERMINATION OF FECAL AMYLASE *

JOHN A. WOLFER, M.D.
Associate Professor of Surgery, Northwestern University Medical School
CHICAGO
AND
L. W. CHRISTIAN, B.S.
DETROIT

At the present time, there are no adequate means of estimating pancreatic function. Many tests have been devised and modified, but sooner or later have been discarded. The chief objection seems to be that clinical diagnoses cannot be confirmed by such tests with any reasonable degree of accuracy.

That several of the present means of estimation are based on sound principles is evident, but entirely too much has been expected of the tests. With the present means, diseases of the pancreas of a mild degree, or relatively nondestructive, cannot be determined.

The probability that the pancreatic tissue is normally present in an amount far in excess of the actual enzyme requirement seems to have been overlooked or disregarded in much of the work that has been done. Criticism that has been offered in connection with the problem has not taken this factor into consideration. It seems likely that the pancreas, as well as other secretory organs, normally secretes amounts in proportion to the needs of the body, and one may as logically assume that a disease process would have to involve a considerable portion of the gland before it would fail to supply the amount of enzyme necessary for digestion. Therefore, any test aimed at the determination of pancreatic hypofunction would show only positive results if sufficient gland substance was involved to overcome the large amount of secreting cells present as a "safety factor," and enough more to cause an actual reduction below the necessary amount.

With this idea in view, it cannot be said that pancreatic function tests being normal, the pancreas is not diseased; only in case there is obstruction to the outflow of digestive enzymes would there be increased diastase in the blood or urine or decreased diastase in the feces or duodenal contents without a considerable portion of the gland being diseased.

* From the department of Surgery and the Laboratory of Surgical Research, Northwestern University Medical School.

Thus the field of pancreatic efficiency tests is, at the present time, limited to a few pathologic conditions and cannot be used as a general routine procedure to differentiate pancreatic lesions from other abdominal conditions.

It is possible that with the culmination of the present work being done on secretin, a satisfactory method can be devised through the estimation of complete activity by specific stimulation and its quantitative estimation through the medium of fecal amylase determinations. With the present methods, the only conclusion that can be drawn from a pancreatic function test is whether or not the pancreas is able to produce sufficient enzyme for normal digestive function, or that there be obstruction to the duct.

METHODS FOR DETERMINING PANCREATIC FUNCTION

Many tests have been devised, but none have been successful to a satisfactory degree. For purposes of discussion a number of them are cited.

Dye Tests.—Giichiro tested nine dyes for selective pancreatic secretion, using dogs with Pawlow fistulas. Methylene blue (methylene chloride, U. S. P.) was secreted in small amounts.

Ivy tried thirty-three dyes, with the result that the pancreas was shown to secrete minute quantities of methylene blue and methyl violet, but not sufficient amounts to be used for quantitative estimation.

Miscellaneous Tests.—Decker used Loewi's test in 500 miscellaneous cases without conclusive results.

Cockcroft used Loewi's epinephrine mydriasis test in two significant cases: 1. A case in which a normal pancreas was found at autopsy gave three negative tests on separate occasions. 2. A case in which the pancreas was found to be almost completely disorganized from malignancy, gave marked positive reactions, the last test being made three days before death. These cases serve to illustrate the absolute inaccuracy of the test.

Lutz expressed the belief that the Bassler test is of great diagnostic and prognostic value, but there is not sufficient evidence to warrant such conclusions. Bassler and Lutz presented a series of ten cases with various degrees of involvement of the gallbladder and pancreas. They claimed to have demonstrated the specificity of the test, but the results are not convincing.

Schmidt devised a test using nuclear digestion as an index. This test shows relatively little, as it is purely qualitative.

Goetz believed that the von Ehrman test is more reliable than determinations of the blood and urine diastase. He believed that the method will show deviations from the normal. The evidence is not conclusive.

Wallis completed an investigation of pancreatic function tests. He reported unfavorable results with an oil test meal (trypsin and diastase determination), Sahli's test, Cammidge test, Koshwadis modification of the Schmidt test and the Sajodin test of Winternitz. He believed that a positive Loewi's test together with diastase in the urine and glycosuria would be a valuable indication. He did not believe that the others were of value.

Estimation of Diastase in Duodenal Contents.—Buckstein (1922) modified the Einhorn test (1912) by using a celluloid capsule attached to a thread which he passed into the duodenum. He reported favorable results, giving the normal value as from 3 to 7 units. Further evidence could not be found to support his method.

Gavrila and Paraschivesco used the method of Einhorn in eleven cases of diabetes mellitus. They believe that the results will not show a parallel with the severity of the diabetes, and, therefore, that it is of little value in this disease.

De Loch modified Einhorn's method, using 30 cc. of tenth normal hydrochloric acid as a stimulus. His claims are too great for the amount of evidence presented.

Whipple minimized the value of the duodenal tube method of determination of enzymes. Grote claimed that the duodenal tube methods are not of value because: 1. The secretion varies in different parts of the duodenum. 2. Ether is not a reliable artificial stimulus. 3. The reaction varies the enzyme activity. 4. Variation of the results in normal persons is too great. Grote expressed the belief that the best way to determine pancreatic function is by a test meal and examination of the stool.

Labbe, Nepveux and Adlersburg (1925) modified the Katch method of injection of ether through the duodenal tube. They gave magnesium sulphate first to evacute the gallbladder, and then ether to stimulate the pancreas. They reported favorable results in three of seven cases.

McClure, Jones, Wetmore and Reynolds (1924) claimed to have established the normal pancreatic enzyme concentration of the duodenal contents. They claimed to show diminution of the enzyme in obstruction and concentration of it in necrosis of the pancreas. Their method seems to be safe in their hands, but unreliable with others.

Determination of Blood and Urine Diastase.—Permin (1924) gave the normal urine diastase value as from 8 to 16 units and reported a case of suppurative cyst of the pancreas with a urinary diastase of 1,024 units. He said that massage of the pancreas and artificial pancreatitis will produce elevated urinary diastase in rabbits.

Von Strasser (1926) gave the figures for normal blood diastase as from 8 to 16 units. He said that any value over 32 is pathologic. A

series of ten patients was used in his determinations. His results, however, are not conclusive.

Moller determined urinary diastase in twenty-three cases in which there was tenderness in the region of the pancreas. He found the diastase present in unusual amounts. Eight cases were proved at operation to be pancreatic disease, but he does not say to what extent the pancreas was found involved.

Markowitz and Hough have shown that after pancreatectomy in dogs the blood diastase is at first increased and then falls to below the highest normal level within twenty hours. They did not see any justification for determinations of the blood diastase in diabetes mellitus.

Diastase in Feces.—Wohlgemuth (1910) gave the average normal value for amylase in feces as $Df\frac{38°}{24h} = 468.75$. The lowest normal values are 100. In one case of obstruction of the pancreatic duct, he reported a fecal amylase of 15.

McClure and Pratt (1917) showed that in obstruction to pancreatic secretion in man and dog there is marked diminution or absence of diastatic activity in feces. They believed, however, that the estimation of fecal amylase is of little value in the clinical diagnosis of pancreatic disease.

Comment.—Dye tests and such miscellaneous tests as have been cited have not proved satisfactory, and results in the hands of others than the original investigators have shown nothing of importance.

Determinations of blood and urine amylase will not show evidence of pathologic process except in obstruction to the outflow of pancreatic secretion. Even then the effect is transitory, as shown by Markowitz and Hough. There is no sound physiologic reason for this determination in other than obstructive cases.

In the estimation of diastase in the duodenal contents, the work of McClure and his associates has been successful to a certain extent. Their work shows that it is only by causing a stimulation to pancreatic secretion and the determination of complete functional capacity that an accurate idea of the state of the pancreas can be determined. Their tests, however, are not satisfactory. Grote has shown that the duodenal tube cannot be relied on to collect uniform samples in all cases. Further, they have not used a specific stimulus, and the test has not shown uniform results in other hands.

Ivy and Koskowski (1926) have shown that there is no compensatory amylase secretion by the succus entericus following pancreatectomy. Wohlgemuth and McClure have both shown that determinations of fecal amylase are of value in determining obstruction to the outflow of pancreatic secretion. Work on other phases of the test has not been done; hence its use in the present work.

It is probable that with the advent of secretin in a purified form, we may be able by its administration to secure complete stimulation to the pancreas and by the determination of amylase in the feces, secure a definite quantitative estimation of the functional capacity of the pancreas. This work awaits a purified nontoxic secretin of known specific action.

FECAL AMYLASE DETERMINATIONS

Amylase is chosen in preference to either of the other two pancreatic enzymes, because: 1. With it the reversibility of the hydrolytic reaction is negligible (Hollander and Marcus—1925). 2. The time law of Hedin can therefore be applied to this reaction. 3. Kjeldahl's law of proportionality may also be applied to diastase (Sherman and Kendall—1910). 4. The enzyme is less effected by outside influences than are lipase and trypsinogen. The feces were used as a source for the amylase in preference to blood, urine or duodenal contents, for these have not proved to be satisfactory, as shown by the review of the literature.

Method.—Hawk (1927) modified the Wohlgemuth test and his modification was used in these determinations. The test is based on the extraction of amylase from fresh feces by a phosphate-chloride buffer solution and the digestion of it in varying amounts against 5 cc. of 1 per cent soluble starch. The digestion is carried out in an incubator at 38 C. for twenty-four hours, and the end-result is determined by the starch-iodine reaction. Details of the technic are given in Hawk's "Physiological Chemistry" (1927).

Twenty-four hours was used in preference to shorter periods for digestive action, for it has been shown that 1 C. variation in temperature will throw the results off 10 per cent when only one-half hour is allowed for digestion (Sherman, Kendall and Clark—1910). The starch-iodine reaction was used in preference to the more careful copper reduction reactions, for while it is not so delicate, it is simple, practical and as accurate as the clinical results warrant. It has the advantage of marking the completion of a fairly definite step in the digestion of starch, whereas the copper reduction method measures the amount of substance or substances produced by successive steps through intermediate products which are but imperfectly known (Sherman, Kendall and Clark—1910).

Phosphate-Chloride Buffer.—Hawk (1911) has modified Wohlgemuth's original method by adding phosphate-chloride buffer solution to the reaction as a diluting medium. Sherman and Kendall (1910) and Hawk (1911) have shown that amylase is not completely activated unless electrolytes are present.

Vernon (1901-1902) and Chittenden and Griswold (1881) have shown that a trace of acid—0.004 per cent hydrochloric acid markedly (four times) activates the enzyme and that lactic acid 0.0083 per cent

increases its activity 4.5 times. Acid of above 0.009 per cent hydrochloric acid inhibits the action of amylase, as does 0.04 per cent lactic acid.

Sedimentation.—The results are in terms of solid fecal sediment to eliminate the bulk of the error that would result from perverted water content due to diarrhea or constipation. This is believed to be better than the old method of desiccation which tends to deteriorate the enzyme.

Acid reaction was checked by titration with tenth normal sodium hydroxide.

Fecal Amylase Determination in Normal Persons.—Since Wohlgemuth's values are dogmatic and do not show whether there is or is not a definite normal variation in diastase content of the feces, it was deter-

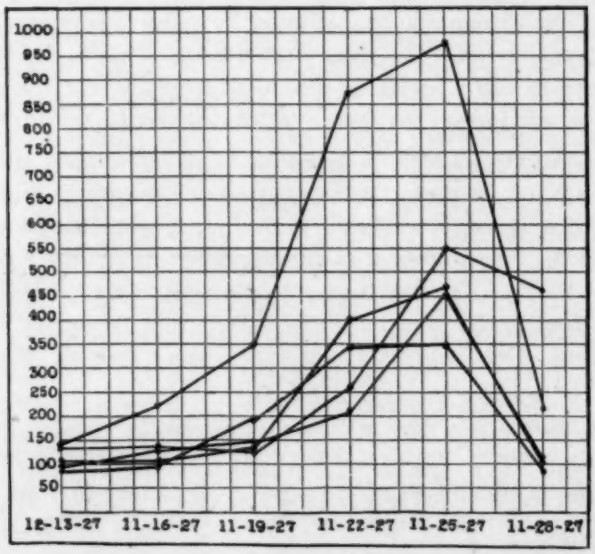

Chart 1.—A graph of the fecal amylase values of normal persons, taken every third day. The values are in terms of $Df\frac{38°}{24\ h}$. $Df\frac{38°}{24\ h}$ = cc. of 1 per cent starch solution digested by the amylase in 1 cc. of centrifugalized fecal sediment at 38 C. in twenty-four hours. This chart shows a definite parallel in the rise and fall of the curves.

mined expedient to run a series of controls. For this purpose medical students, two groups of five each, were selected. These men ate their meals at the same fraternity house table, and, with the exception of candy, peanuts, etc., the diet was essentially the same.

Series 1: Five men, under the conditions already described, participated in this series. The stools were examined for diastase content every third day for eighteen days (chart 1). The results are shown in table 1.

It can be seen from the graph in chart 1 that while there is some slight variation, the diastase seems to vary as the diet and in the same

person may cover a wide range of values, depending on the food intake. As the direction of variation is parallel in practically all cases, we may assume that a given diet has practically the same stimulating effect on the pancreas in all normal persons. None of the values as shown in table 1 fell below the value of Df. $\frac{38^{\circ}}{24h} = 91$. It is conceivable that a healthy person receiving an average diet should not have a normal value below 90, which value is ten points below the lowest normal value as determined by Wohlgemuth.

Series 2: Another group of five medical students participated in this series under the same conditions as those in series 1. Fecal amylase was determined daily for one week, to show the day to day variation (chart 2). The results are shown in table 2.

TABLE 1.—*Data on Series 1* *

Patient	Nov. 13	Nov. 16	Nov. 19	Nov. 22	Nov. 25	Nov. 28	Average
G.	145	226	350	876	981	222	466
D.	99	126	133	210	476	110	192
M.	91	97	180	342	345	102	193
R.	101	102	127	400	460	96	216
B.	143	131	120	264	547	461	277

* The foregoing values are in terms of Df $\frac{38^{\circ}}{24\,h}$. A graph of these figures is shown in chart 1.

TABLE 2.—*Data on Series 2* *

Patient	Dec. 1	Dec. 2	Dec. 3	Dec. 4	Dec. 5	Dec. 6	Dec. 7	Average
W.	400	125	91	423	190	793	91	302
C.	871	782	473	732	257	476	168	537
T.	400	221	143	778	118	1,130	472	504
B.	386	200	250	732	91	1,087	530	468
R.	520	260	250	836	200	1,110	420	513

* The values in this table are in the same terms as those in table 1.

Again it will be seen that a close parallel exists between the values, although the variation from day to day in the same person occurs through a wide range. Again we assume that the main factor in this variation is diet.

From this series, the following conclusions were made: 1. The amylase output of the pancreas varies from day to day, depending largely on the intake of food.

2. The value for persons on the same diet is relatively the same on the same day.

3. The normal average varies from 302 to 537, with Df. $\frac{38^{\circ}}{24h} = 465$ as the normal average. This value is close to that set by Wohlgemuth (468.75).

4. It is logical to assume that persons with various degrees of pancreatic disease might show low values because of low food intake

rather than because of pancreatic deficiency. This factor must be taken into account in evaluating clinical results.

5. It is reasonable to believe that this test used clinically can become effective only if the patients are placed on a uniform, quantitative and qualitative diet.

Series 3: A third series of five students was used under conditions similar to those in series 1 and 2, except that the total stool was saved for each twenty-four hours for seven consecutive days.

Determinations of amylase in twenty-four samples necessitated a slight modification of the previously described technic, as follows:

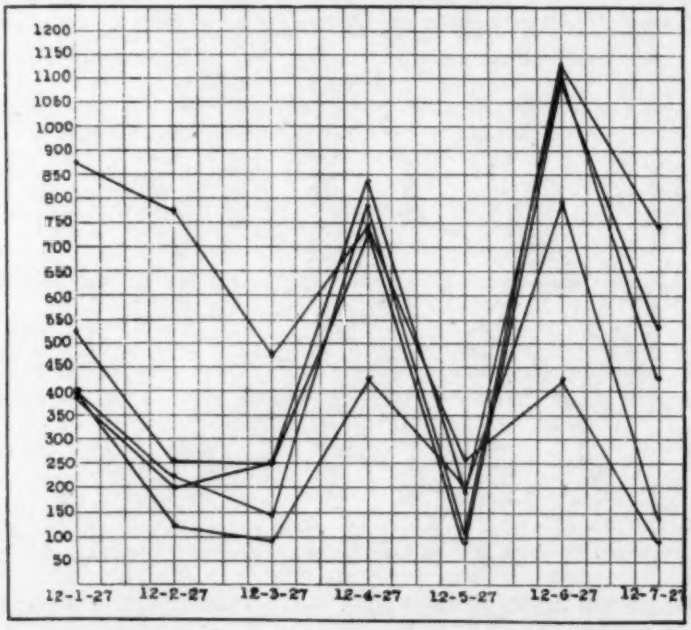

Chart 2.—A graph of the fecal amylase values of normal persons, showing weekly variation. The values are in term of $Df\frac{38°}{24\ h}$. This chart also shows a distinct parallel in the rise and fall of the curves.

1. The twenty-four hour stool specimen was placed in a 1.5 liter granite bowl, and sufficient phosphate-chloride buffer solution was added to make 500 cc.

2. The mixture was thoroughly stirred, any mechanical contrivance at hand being used, such as a pestle, egg-beater or anything which would aid in securing a mixture of uniform consistency.

3. The mixture was allowed to digest for one-half hour, being stirred occasionally.

4. A 15 cc. representative portion was measured out and placed in a graduated centrifuge tube and centrifugalized for fifteen minutes.

5. From this point, the technic was the same as that of the Wohlgemuth-Hawk method already described, except that the final reading was in terms of the amount of standard 1 per cent starch solution—in liters—that will be digested by all the amylase in the twenty-four hour specimen.

The results are shown in table 3 and chart 3.

From table 3 and chart 3, it can be seen that there is no constant relation between the amount of amylase in twenty-four hour specimens, either of persons on the same diet or of the same person from day to day, although the weekly totals approximate each other rather closely.

It seems logical to conclude that the motility of the gut affects the total twenty-four hour output, and that there is a wide margin of individual variation due to innumerable factors. From the previous series, it does not seem that gastric motility affects the amount of amylase in any

TABLE 3.—*Data on Series 3*

Patient	Dec. 1	Dec. 2	Dec. 3	Dec. 4	Dec. 5	Dec. 6	Dec. 7	Total Output
W.	26.80	3.3	13.00	6.65	33.3	55.0	6.65	144.40
C.	6.65	55.0	26.80	26.80	13.3	27.3	26.80	182.65
T.	13.30	33.3	3.30	13.30	55.0	3.3	33.00	154.50
B.	12.80	27.3	6.65	13.30	13.3	33.3	6.65	113.50
R.	27.80	26.8	33.00	3.30	12.8	13.3	26.80	143.80

The results in this table are in terms of liters of standard starch solution (1 per cent) which will be digested by all the amylase in the twenty-four specimen.

one average selected portion of stool of persons on the same diet at the same time. It seems most likely that the amylase present in a unit volume varies as the food intake and not with gastric motility, the values being in terms of solid fecal sediment. It is probable that equal portions of the same kind of food will stimulate the pancreas to secrete a definite amount of amylase in all normal persons and that its mixture with that portion of food will be relatively the same concentration, the factor of water dilution being removed.

CLINICAL INVESTIGATION

Previous Work.—Considerable work has been done on the determination of pancreatic enzymes as an index to pancreatic disease. A few examples have been selected from the literature.

Wallis (1920), from a study of eight cases of acute pancreatitis, twenty-eight cases of chronic pancreatitis, five cases of carcinoma of the head of the pancreas, twenty cases of disease of the liver and thirteen miscellaneous cases, concluded that he could diagnose pancreatic disease if Loewi's test, glycosuria and increased diastase in the urine all showed positive results. Confirmation of his work was not found.

Isaacs and Kreiger studied thirty cases of achlorhydia and did not find abnormality in distase. They concluded that there were normal diastase values in cases of "gastrogenous diarrhea."

McClure, Jones, Wetmore and Reynolds (1924), from a study of diastase in duodenal contents, concluded:

1. Chronic pancreatitis shows depressed diastase values.

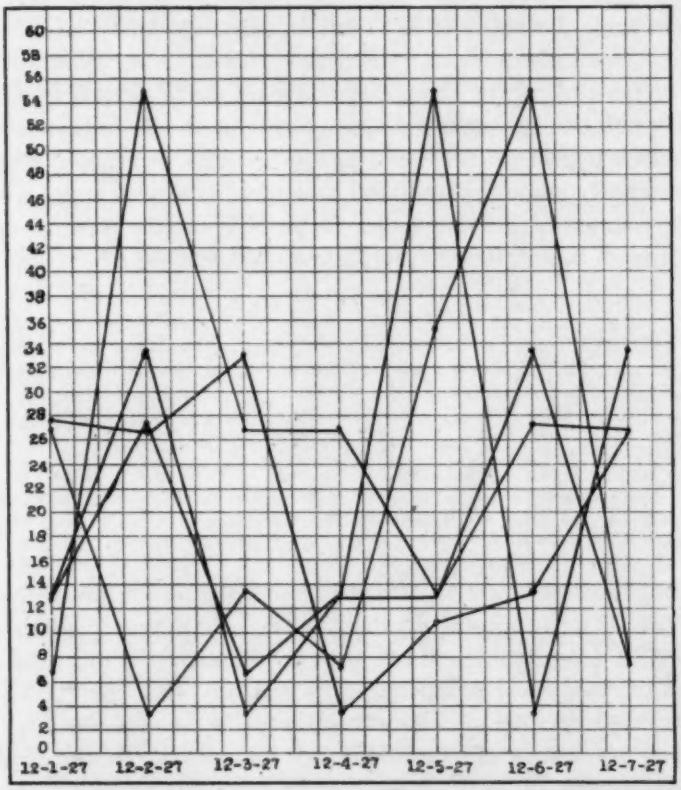

Chart 3.—A graph of the total fecal amylase in twenty-four hour specimens from normal persons, the determinations being made on seven consecutive days. The values are in terms of liters of 1 per cent starch solution digested by the amylase in the twenty-four hour specimen of stools. This chart shows the marked variations in the amount of amylase in the twenty-four hour specimens either of persons on the same diet or of the same persons from day to day. There is not a suggestion of a parallel in the curves.

2. Acute pancreatic necrosis and carcinoma of the pancreas show abnormal (?) values.

3. Obstruction to the outflow of pancreatic enzyme shows diminished or absent values.

4. Necrosis shows concentration of the enzyme.

McClure, Montague and Mortimer (1924), also McClure, Jones and Chester (1922) concluded that patients with achylia gastrica have normal pancreatic function as determined by diastase in the duodenal contents.

Labbe, Nepveux and Adlersburg (1925), from a study of duodenal content diastase, concluded that:

1. Diastase was decreased in patients with cholelithiasis as well as in destructive lesions of the pancreas.

TABLE 4.—*Data on Fecal Amylase Determinations in Clinical Cases*

No.	Patient	Age	Disease	38° Df. — 24 h.	Sex
1	C. K.	68	Chronic cholecystitis with stone, proved	335.0	F
2	M. S.	34	Chronic cholecystitis with stone, proved	57.1	F
3	C. P.	25	Chronic cholecystitis with stone, proved	107.0	M
4	M. L.	43	Chronic cholecystitis with stone, proved (with pancreatitis)	246-201	F
5	E. K.	48	Chronic cholecystitis with stone, proved (stone in ampulla with obstructive jaundice)	52.6	F
6	S. M.	46	Chronic cholecystitis with stone, not proved	71.1	M
7	D. S.	36	Chronic cholecystitis with stone, x-ray positive	100.0	F
8	E. L.	28	Common duct stone, not proved	322.0	F
9	E. E.	50	Chronic cholecystitis, proved (diffuse sclerosis of pancreas)	60.0	F
10	C. K.	..	Chronic cholecystitis, proved	238.0	F
11	I. W.	..	Chronic cholecystitis, not proved	62.4-62.5	F
12	J. K.	24	Chronic cholecystitis, not proved	92.5-36.9	M
13	M. E.	..	Chronic cholecystitis, not proved	22 -26.3	M
14	J. N.*	36	Chronic diffuse pancreatitis, with obstruction	16.8	M
15	S. S.	38	Chronic diffuse pancreatitis	20.0	F
16	M. C.	58	Carcinoma of head of pancreas	100.0	F
17	F. D.	43	Chronic nonulcerative colitis	62.5	M
18	J. H.	34	Chronic nonulcerative colitis	335.4	M
19	C .S.	32	Chronic nonulcerative colitis	57.1-117.6	M
20	J. G.	41	Sprue	100-103.7	M
21	M. H.	38	Acute yellow atrophy of liver	62.5	F

* Case 14 (J. N.) came to autopsy on July 19, 1928. The right one third of the pancreas was replaced by carcinoma, the middle third contained little normal gland tissue and consisted essentially of carcinoma. The left third was extensively infiltrated by connective tissue with marked diminution of gland tissue. The duct was virtually obstructed by a carcinomatous nodule growing into the ampulla of Vater. A fine probe could be forced through the opening. The duct of Santorini was obliterated. The pathologist's opinion was that 90 per cent of the gland had been destroyed. The low fecal amylase values are therefore significant.

2. They also found decreased diastase in three of seven patients with diabetes mellitus.

Bassler and Lutz (1925), using Bassler's test, analyzed ten cases and concluded:

1. Chronic cholecystitis, especially with stone, shows a low value (from 2 to 7 units).

2. One case of carcinoma of the gallbladder and pancreas showed a negative test.

Cockcroft (1920), in direct contradistinction to Bassler and Lutz, using the same tests, found destructive lesions showing a positive reaction, while a case in which the pancreas was normal showed a negative test several times.

Gavrila and Paraschivesco (1926), using the method of Einhorn, analyzed eleven cases of varying degrees of diabetes mellitus and concluded that the diminution of pancreatic secretion is not parallel to the severity of the diabetes.

Landan, Cygielstrejck and Fejgin (1926) found four cases of achylia gastrica associated with "pancreatic achylia." The patients had pernicious anemia, and the authors suggested that the pathologic process in these two organs may be part of the clinical picture of the disease.

Silverman (1927), determining duodenal diastase, concluded that sprue shows normal pancreatic ferments. Manson-Bahr demonstrated histologically for him that the histologic structure of the pancreas was normal in this disease.

Clinical Cases.—Determinations of fecal amylase were made in a series of cases including four cases of known chronic pancreatitis, proved at operation; five cases of chronic cholecystitis with stone, proved at operation; two cases of chronic cholecystitis with stone, not proved by operation but clinically positive; two cases of chronic cholecystitis-noncalculus, proved at operation; three cases of chronic cholecystitis, not operated on but clinically positive; one case of stone in the common duct in which the gallbladder had previously been removed, not proved at operation but clinically positive; and five miscellaneous cases.

These patients were placed for twenty-four hours on a fixed diet, as follows:

Breakfast:
Dish of oatmeal (about two-thirds cupful)
Toasted white bread (one slice)
Whole milk (8 ounces)

Dinner:
Buttered white bread (one slice)
Whole milk (8 ounces)
Lean steak (6 ounces)
Boiled potato (1 medium sized)
Corn starch pudding (two-thirds cupful)

Supper:
Toasted white bread (one slice)
Whole milk (8 ounces)
One poached egg
Corn starch pudding (two-thirds cupful)

The first stool specimen, passed twenty-four hours after the last meal of the diet, was saved and the fecal amylase determined after the method of Wohlgemuth-Hawk, as in series one and two of the normals.

Although many of the foregoing values are below the lowest values (91) found in the normal series, operation confirmed gross changes in

the pancreas in only three cases. Lack of operation in several cases deprived us of confirmative evidence. We cannot, therefore, say that values below 91 are indicative of pancreatic disease. E. K. (case 5) had a stone in the ampulla of Vater and J. N. (case 14) a diffuse pancreatitis with obstruction of the duct, each with jaundice, and the low amylase values were probably due to obstruction to the outflow of pancreatic juice, although in case 14 there was an extensive change in the pancreas.

The case of carcinoma of the head of the pancreas (M. C.) shows the lowest normal level, and it is likely that an insufficient amount of pancreatic tissue was involved to decrease the amount of secretory cells below the actual dietary requirements. In this case, there was no evidence of obstruction of the duct.

TABLE 5.—*Dextrose Tolerance Test in Cases 4 and 9*

Case 4		
Fasting sugar	140	Urine sugar negative
First hour	155	Urine sugar plus with 15 drops
Second hour	151	Urine sugar two plus with 15 drops
Third hour	148	Urine sugar plus with 15 drops
Fourth hour	...	Urine sugar negative
Case 9. Before cholecystectomy		
Fasting blood sugar	96.0	Urine sugar negative
First hour	164.0	Urine sugar negative
Second hour	164.0	Urine sugar, trace
Third hour	127.5	Urine sugar negative
161 days after cholecystectomy		
Fasting blood sugar	98.0	Urine sugar negative
First hour	201.0	Urine sugar, 0.17 per cent
Second hour	269.4	Urine sugar, 7.1 per cent
Third hour	243.9	Urine sugar, 5.6 per cent

Of the three cases of proved nonobstructive pancreatitis, all of long duration, two showed values considerably below the lowest normal level (20 and 60). There was much more extensive involvement of the pancreas in these two than in the third (case 4, M. L.), in which the process was mostly confined to the head of the organ, and in which the values were well within the normal (246 and 201). Dextrose tolerance determinations were made in these cases with the result that the tests would further indicate that the secretion of the pancreas is diminished more in cases 9 and 15 than in 4.

In case 15, the patient had active diabetes, so a sugar tolerance test was not attempted.

The case of limited pancreatic involvement seems to demonstrate that unless the changes in the pancreas are marked, it will secrete, under normal stimulus, sufficient enzyme to digest normal food intake. The results of Brown parallel these observations.

In the three cases of chronic nonulcerative colitis showing varying degrees of amylitic activity, conclusions cannot be drawn. It was

thought that the cases of colitis might show an excess of acid in the stools and thus inhibit amylitic activity (Vernon), but amylase determined with the buffer solution as the diluting medium showed practically normal reactions. The Vernon theory of acid inhibition cannot here be displayed, for an excess of acid was not present.

In the case of sprue (case 4, J. G.) there was no decrease in fecal amylase value (100 and 103.7), which confirms the conclusion of Silverman.

In the case of acute yellow atrophy of the liver with changes in all the abdominal organs (determined at autopsy three days after the test), a value of 62.5 was found, which is below the lowest normal value—91. This may have been due to destructive changes in the pancreas, with actual decrease in the necessary amount of secreting tissue.

Conclusions.—1. Cases of obstruction to the duct will show a decrease in fecal amylase (confirmed by McClure).

2. Cases in which there is diffuse involvement of the pancreas, such that it cannot supply sufficient amylase for normal digestive processes, will show decreased fecal amylase.[1]

3. At the present time, cases with mild involvement of the pancreas cannot be confirmed by determinations of fecal amylase, probably owing to the "safety factor" of secreting tissue normally present.

4. It may be that with larger series of cases of carefully conducted clinical experiments, the same diet being used in all cases, we may be able to demonstrate cases with mild involvement of the pancreas.

ANIMAL EXPERIMENTS

Four dogs were prepared as follows: A short loop of bowel, from 15 to 20 inches (37.5 to 50.8 cm.) from the tail of the pancreas, was transplanted underneath the skin of the abdominal wall, just lateral to the umbilicus. Several days later, a fistula was made into this loop. The dogs so prepared were used as follows:

Dog 1.—This animal was fed a daily meal of 800 cc. of meal mash and 300 Gm. of bread. Three times weekly, beginning fifteen minutes after the meal was eaten, 10 per cent sodium bicarbonate solution was allowed to perfuse through the bowel by means of a gravity bottle and dropping tube which was connected by a catheter (no. 14 F.) passed into the distal portion of the transplanted loop such that 500 cc. will pass through in one hour. Fecal amylase determinations were done on the two specimens of feces passed following such perfusion. Results are shown in table 6.

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1. A case of hyperinsulinism due to a carcinoma of the pancreas metastasizing into the liver is now under study. Fecal amylase values are from 110 to 80; the total for the twenty-four hour specimen is 6.65. The blood sugar at the time of amylase determinations was 0.049. This patient does not exhibit any signs of obstruction of the duct and no doubt the pancreatic "safety factor" is encroached on at the present time, as an amylase value of 80 is below our normal standard.

Dog 2.—This animal was fed the same as dog 1. The perfusion was done in the evening from about eight to ten hours after the ingestion of the meal. The results are shown in table 7.

In the case of each dog, it was found that in amounts up to 150 cc., the alkaline perfusion was well tolerated. If greater amounts than this were used, the dog salivated, became nauseated and vomited from 10 to 20 cc. of the meal. In the case of dog 2, which was given the perfusion several hours after the meal, nausea was present after 150 cc., but the dog did not regurgitate although reverse gastric peristalsis seemed to be present at intervals.

TABLE 6.—*Data on Dog 1*

Date	Cc. of 10% $NaHCO_3$	Amylase Df $\frac{38°}{24\ h}$ First Specimen	Second Specimen	Control
3/26	...	...	.....	444
3/31	100	782	1,540	...
4/ 1	...	...	.....	236
4/ 2	150	471	1,020	...
4/ 4	150	160	1,810	...
4/ 7	200	812	2,034	...
4/ 8	...	...	.....	264
4/ 9	250	1,026	1,760	...
4/11	...	.....	.....	194
4/14	Dog is quite sick, refuses to eat; perfusion stopped			

TABLE 7.—*Data on Dog 2*

Date	Cc. of 10% $NaHCO_3$	Amylase Df $\frac{38°}{24\ h}$ First Specimen	Second Specimen	Control
4/11	...	...	.....	790
4/14	150	530	1,712	...
4/15	...	...	.....	380
4/16	150	664	1,830	...
4/18	150	260	1,960	...
4/21	200	540	1,836	...
4/22	...	...	.....	218
4/23	300	370	2,108	...
4/25	350	516	1,810	...
4/28	400	226	2,332	...
4/29	...	...	.....	280
4/30	400	862	2,279	...

In all cases, the first stool after the perfusion was soft and bulky and usually was passed within one hour. The second stool was passed from twelve to eighteen hours later and was normal in appearance. Fractions that amounted to less than five points were dropped from the results shown in the tables.

Dogs 3 and 4.—These animals were fed meals the same as dogs 1 and 2. From about eight to ten hours after the meal, the bowel was perfused with 1.25 per cent lactic acid. One attempt was made to perfuse during the ingestion of a meal, but 2.5 per cent lactic acid was used and after 150 cc. had been given, the dog vomited a large portion of the meal. Thereafter perfusions were given at night as already stated. The results are shown in tables 8 and 9.

Farrell and Ivy have shown in dogs with pancreatic transplants and Thiry fistulas that:

1. Administration of 150 cc. of tenth normal hydrochloric acid markedly stimulated the pancreatic secretion.

2. One hundred and fifty cubic centimeters of water or 0.3 per cent sodium carbonate stimulated secretion but to a milder degree, the carbonate being less active than water.

Our results on experimental work done show:

TABLE 8.—*Data on Dog 3*

Date	Cc. of 1.25% Lactic Acid	Amylase Df $\frac{38°}{24\ h}$ First Specimen	Second Specimen	Control
5/ 2	...	.....	.....	581
5/ 5	100	1,032	3,276	...
5/ 7	150	976	4,800	...
5/ 9	150	1,248	5,569	...
5/12	200	630	5,827	...
5/14	250	460	6,410*	...

* This value may have been higher as it was the last tube in the series.

TABLE 9.—*Data on Dog 4*

Date	Cc. of 1.25% Lactic Acid	Amylase Df $\frac{38°}{24\ h}$ First Specimen	Second Specimen	Control
5/14	...	.....	.....	370
5/16	100	.....	2,710	...
5/19	150	1,810	3,276	...
5/20	150	1,712	2,634	...
5/21	150	1,248	4,896	...
5/23	200	.....	5,569	...
5/24	200	1,032	5,569	...
5/25	250	976	5,827	...

1. The administration of 1.25 per cent lactic acid (from 100 to 250 cc.) through a jejunal fistula markedly stimulates pancreatic secretion, and the stimulation is progressively greater as the amount given increases. Such increases can be demonstrated by the quantitative determination of fecal amylase.

2. The administration of 10 per cent sodium bicarbonate solution (from 100 to 400 cc.) markedly stimulated the secretion of the pancreas although to a lesser degree than does 1.25 per cent lactic acid. This increased secretion can also be demonstrated by fecal amylase determinations.

3. It is probable that the determination of fecal amylase will serve as a satisfactory method of determining pancreatic secretion when a specific stimulator that will produce complete uniform stimulation has been devised.

SUMMARY

1. The majority of the literature on pancreatic function tests has been reviewed, and some of the more important conclusions have been stated in this paper.

2. Determinations of fecal amylase were made on a series of normal persons to determine the normal value and its relation to the various factors concerned.

3. An attempt was made to establish a normal twenty-four hour fecal amylase value. The attempt was unsuccessful.

4. A series of cases was investigated and determinations of fecal amylase were made. Such conclusions as were evident have been stated in the foregoing work.

5. Animal experimentation was done to show that pancreatic stimulation can be demonstrated by determinations of fecal amylase.

CONCLUSIONS

1. Fecal amylase values of normal persons, using the Wohlgemuth-Hawk test, vary widely from day to day, depending largely on the diet.

2. In normal persons, the same diet produces closely similar stimulation to pancreatic secretion as shown by the values given on the same day by different persons on the same diet.

3. The weekly quantity of amylase secreted by normal persons on the same diet, as determined by determinations of fecal amylase, approaches a uniform value. That this is not a desirable procedure for clinical use, is evident.

4. The determinations of fecal amylase, Wohlgemuth-Hawk method, will show clinical results in only two types of cases: (*a*) cases of obstruction to the outflow of pancreatic juice; (*b*) cases in which a large portion of the gland is diseased so that it cannot supply sufficient amylase for normal digestive needs.

5. The determination of fecal amylase in dogs will show a quantitative increase in pancreatic secretion after gland stimulation by the application of lactic acid or sodium bicarbonate to the jejunum.

6. It is probable that a successful determination of fecal amylase can be devised, so that it will be of value in determining mild degrees of pancreatic involvement if the present work on secretin produces a purified, nontoxic product that can be used as a uniform stimulus for maximum pancreatic secretion; such maximum secretion to be determined by estimations of fecal amylase.

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THE CAUSE OF DEATH IN HIGH OBSTRUCTION*

HENRY S. F. COOPER, M.D.
NEW YORK

What is the cause of death in high obstruction?

Why is it that a simple obstruction of the large intestine is compatible with life for a long time, while obstruction of the small intestine is rapidly fatal?

A tremendous amount of work has been done on this subject, which in turn has given rise to a multitude of theories, hardly two of which coincide. As in all problems for which a great number of explanations are offered, it is safe to assume that no one of them is entirely correct. Also, no theory has given rise to any practical means of preventing death after the condition has once fully established itself. In other words, no real advantage to the patient has accrued from this great mass of work. All medical and surgical research should have practical application as its ultimate goal. This goal is still in the dim distance as far as the work on high obstruction is concerned. Now, as always, prompt surgical intervention is the only means of combating this condition, and only too often this is of no avail.

The cause of death in high obstruction is not known. The object of this article is not to advance any one theory above the others; rather, is it an effort to present the subject in its many different phases and from its many different angles with the hope that somebody will see the spark and fan a flame that will bring light where there is darkness.

CLINICAL AND PATHOLOGIC PICTURE

Patients suffering from uncomplicated obstruction of the small intestine rarely survive more than six or eight days if early surgical intervention does not take place. When the picture is fully developed, the following outstanding features present themselves:

The patient's psychology is often misleading. He is mentally alert and acutely aware of his surroundings. He does not realize the seriousness of his condition unless he is told. When first seen he is usually tossing about in bed. He is apt to talk about trivialities and make plans for the future. I have seen patients leave the hospital in this condition against the physician's advice.

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* From the Department of Surgical Research, Cornell Medical School, New York.

* This work was aided by a gift of Mrs. John L. Given in support of surgical research.

The patient usually looks acutely ill. His cheeks are sunken; his eyes are bright. In the later stages, he presents the typical hippocratic facies. There are beads of perspiration on his forehead. He often shows fibrillary twitchings of the hands and feet. His extremities are cold and clammy and his lips and nail-beds are often cyanotic. Usually, a deep coma intervenes before death.

Vomiting is a constant symptom. The vomitus first consists of gastric and duodenal contents and later takes on a fecal character, being light brown and of foul odor. At first the vomiting is accompanied by retching, but later it is passive, the material merely spilling from the patient's mouth. Persistent hiccups are often a distressing complication.

He may pass feces and gas in the early stages, but this soon gives way to persistent constipation.

The temperature is normal or subnormal; the pulse weak and rapid; respirations, shallow, and the blood pressure, low.

The red blood count is normal or increased, depending on the dehydration. There is leukopenia. The chemical examination of the blood gives a characteristic picture. The nonprotein nitrogen is high. This rise is almost entirely due to a marked rise in the urea. There may also be a rise in the creatinine. The chlorides are reduced. The carbon dioxide combining power is increased.

The urine is usually scanty, and often shows a trace of albumin or a few casts. The nonprotein nitrogen in the twenty-four hour specimen is much increased quantitatively, being often four or five times the normal amount. The chloride excretion is greatly reduced. The kidney function, as shown by the phenolsulphonphthalein test, is normal or slightly decreased.

The pathologic picture is curiously devoid of positive observations. The outstanding feature is marked splanchnic engorgement. The intestine, if not ruptured, is much dilated above the obstruction; its wall is dusky red and may present areas of gangrene. The lumen is full of stinking reddish-brown fluid which is rich in bacterial content. The mucosa is deeply injected and presents ulcerations. This condition is most marked immediately above the obstruction. Histologically, the intestinal wall shows marked capillary engorgement and areas of necrosis. Some observers have described fatty changes in the liver and evidences of toxic nephritis. These observations are not constant.

I shall next consider the experimental field. Before proceeding any further, it would be well to bring out the difficulties of animal experimentation. It is safe to assume that the condition can be reproduced in animals and that the picture is similar. Dogs lend themselves best to this type of experimentation. Cats and rabbits have been used, but the former are too resistant to the condition and the latter are too delicate. There is a great variation, however, in individual animals. Furthermore, animals in different localities seem to react differently.

There also are seasonal variations. For these reasons, it is not well to attach too much importance to minor differences in the length of survival. One animal that survives indefinitely is worth more as evidence than a hundred that survive a few days more than the normal span of life for the condition.

In order to have a working hypothesis it is first necessary to assume certain facts as established beyond a reasonable doubt. From a review of the literature on experimental work, it seems safe to concede the following facts:

FACTS OBTAINED FROM EXPERIMENTAL WORK IN THE LITERATURE

Fact 1.—Simple obstruction of the duodenum at a point just below the openings of the pancreatic and common bile ducts causes the most acute onset of symptoms and the earliest death. The length of survival and the acuteness of symptoms produced at other points in the small intestine is proportional to their proximity to this point.

Maury [1] was the first to demonstrate this fact. He established what he called the lethal line 35 cm. from the pylorus in dogs. Obstruction proximal or distal to this line he found to produce acute symptoms in proportion to its proximity. Incidentally, the line was below the openings of the pancreatic and common bile ducts. This was established on a series of over 400 animals.

Bunting and Jones [2] confirmed in substance these observations of Maury. Experimenting with rabbits, they found obstruction at the pylorus compatible with life for from thirty-six to forty-eight hours, while obstruction at points from the upper third of the duodenum to the middle of the jejunum caused death in from fifteen to twenty-four hours. Lesions at points below that gave progressively increasing lengths of survival.

Auché,[3] Dragstedt, Moorhead and Burcky,[4] Eisberg,[5] Sugito,[6]

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1. Maury, J. W. D.: Is Death in High Intestinal Obstruction Due to Absorption of Bile? Ann. Surg. **46**:556, 1907; Death in Acute Intestinal Obstruction and Kindred Conditions is Due to Physiologic Disturbance: Study I. Has the Duodenum a Toxic Intestinal Secretion? J. A. M. A. **54**:5 (Jan. 8) 1910.

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Whipple and his co-workers [7] and many others have agreed in general with this, but have been content with stating that the higher the obstruction the more rapidly fatal the outcome.

Fact 2.—Experimental animals suffering from high obstruction show the following clinical picture:

(1) They vomit.
(2) They become dehydrated.
(3) They show tremors and weakness of the hind legs.
(4) The pulse becomes weak and rapid.
(5) The blood pressure falls.
(6) The urine is scanty.
(7) Coma precedes death.

All these symptoms have been so frequently observed that it does not seem necessary to quote references.

Fact 3.—A study of the clinical pathology of animals suffering from obstruction shows the following picture:

Blood:

(1) Leukopenia.
(2) Slightly increased fibrin.[8]
(3) High nonprotein nitrogen, almost entirely due to an increase in urea.
(4) Low chloride content.
(5) High carbon dioxide combining power.

Urine:

(1) Scanty.
(2) Slight trace of albumin.
(3) Nonprotein nitrogen excretion much increased.
(4) Low chloride excretion.
(5) Trace of phenol and indican.

With the exception of item 2 in the description of the blood, all the items are based on the observations of many workers.

Fact 4.—An animal that has died of high obstruction shows the following pathologic picture:

Central Nervous System: Normal, grossly and microscopically.
Lungs: Normal, grossly and microscopically.
Heart: Normal, grossly and microscopically.
Blood Vessels: Williams reported [9] hemolytic staining of the intima of the arteries.

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Stomach: Dilated. Draper [10] and Hartwell and his co-workers [11] reported much capillary dilatation of the mucosa.

Small Intestine: There is marked splanchnic congestion. The portion above the obstruction is dusky red and much dilated. It contains large amounts of foul-smelling, red-brown fluid which is rich in bacteria. The mucosa is greatly injected all the way from the point of obstruction to the pylorus, presenting ulcerations and necrotic areas. Histologic examination shows round cell infiltration and hemorrhages (Hartwell and his co-workers [11]). The pathologic process is most marked just above the obstruction. The intestine below the obstruction is collapsed, but otherwise normal. Hartwell and his co-workers [11] also reported acute hyperplasia of the lymph follicles.

Peritoneum: Normal.

Large Intestine: Draper [10] described much capillary dilatation about the terminal colon. Nobody else reported this.

Liver: Hartwell and his co-workers [11] and Whipple and his co-workers [7] reported occasional congestion and fatty changes.

Pancreas: Hartwell and his co-workers [11] reported congestion. All other investigators reported the pancreas to be normal.

Kidneys: Brown, Eusterman, Hartman and Rowntree [12] reported evidence of severe toxic nephritis although they did not say what this evidence was. Hartwell and his co-workers [11] reported marked congestion and the presence of granular coagula in the tubules. South and Hardt [13] reported cloudy swelling. Draper [10] and Whipple and his co-workers [7] reported normal kidneys.

Spleen: South and Hardt [13] reported the spleen to be swollen. All others reported it to be normal.

There is not by any means a unanimity of opinion on this subject, but nevertheless, it was felt best to include the pathologic description under the facts.

Fact 5.—If a segment of small intestine is isolated and the ends inverted, and if then the continuity of the intestinal tract is reestablished by anastomosis, the animal will present a picture in a general way similar to an obstruction at the level from which the segment was isolated.

This fact was first brought out clearly by Whipple and his co-workers [7] and has been confirmed by many investigators since, most

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prominently by Bunting and Jones,[14] Dragstedt, Dragstedt and co-workers,[15] Eisberg,[5] and Murphy and Brooks.[16]

The statement was made that the picture, in a general way, was similar to that in obstruction. The following variations occur:

1. Colonic and low ileal closed loops are compatible with life indefinitely (Halsted, von Baracz, quoted from Hartwell and his co-workers,[17] Murphy and Brooks,[16] Whipple [18] and Wilkie [19]).

2. The length of the closed loop brings in another factor. Animals with short loops die sooner than those with long ones (Brooks and his co-workers,[20] Dragstedt, Dragstedt and co-workers [21]).

3. Sometimes an animal will survive indefinitely with a closed loop no matter where it is (Dragstedt, Dragstedt and co-workers,[4] Sweet [22]). It seems as if this would have to be laid to individual variation. An animal has never survived when the closed loop received the secretion of the liver and pancreas.

4. Animals with closed loops show a slightly different picture from animals with simple obstruction. They do not vomit as much, they do not become as dehydrated (Ingvaldsen and co-workers [8] and others), and the changes in the blood and urine chemistry are not as marked. Copher and Brooks [23] reported cases of dogs dying without changes.

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20. Brooks, B.; Schumacher, H. W., and Wattenberg, J. E.: Intestinal Obstruction: An Experimental Study, Ann. Surg. **67**:210, 1918.

21. McClintock, J. T.; Dragstedt, L. R., and Dragstedt, C. A.: Some Results from the Experimental Study of Intestinal Obstruction, J. Iowa State M. Soc. **9**:8, 1919.

22. Sweet, J. E.: The Pancreas and High Intestinal Obstruction, Penn. M. J. **19**:492, 1915-1916. Sweet, J. E.; Peet, M. M., and Hendrix, B. M.: High Intestinal Stasis, Ann. Surg. **63**:720, 1916.

23. Copher, G. H., and Brooks, B.: Intestinal Obstruction: An Experimental Study of the Therapeutic Value of the Administration of Sodium Chloride, Ann. Surg. **78**:755, 1923.

Whipple and his co-workers [24] did many experiments in which they demonstrated a rise in the urea. Gatch, Trusler and Ayers [25] reported a slight fall in the chlorides. Nobody else reported any change in the chlorides or in carbon dioxide combining power.

Fact 6.—If there is an interference in the circulation at the point of obstruction (i.e., strangulation), the picture is much more acute and death much more rapid.

The great difference between strangulation and simple obstruction has been recognized by many workers (Brooks and co-workers,[20] Foster and Hausler,[26] Hartwell and his co-workers,[27] Howell,[28] Murphy and Vincent,[29] Reichel,[30] Sugito [6] and Wilkie [31]).

Whether or not high strangulation is more fatal than low is not so clearly demonstrated; however, it probably is. This is difficult to demonstrate because the symptom complex is so acute that the picture is telescoped in as far as time is concerned, and therefore variations in the length of survival are correspondingly more difficult to demonstrate. However, a few references to it are found in the literature (Scholefield,[32] Schönbauer [33]).

There are further variations in the clinical aspect that are similar to, but more marked than, those described under fact 5.

1. The shorter the strangulated segment, the more rapid is the onset of symptoms and the more fatal the outcome (Brooks and his co-workers,[20] Scholefield,[32] Sugito [6]).

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24. Cooke, J. V.; Rodenbaugh, F. H., and Whipple, G. H.: Intestinal Obstruction: VI. A Study of Noncoagulable Nitrogen of the Blood, J. Exper. Med. **23**:717, 1916.

25. Gatch, W. D.; Trusler, H. M., and Ayers, K. D.: Acute Intestinal Obstruction: Mechanism and Significance of Hypochloremia and Other Blood Chemical Changes, Am. J. M. Sc. **73**:649, 1927.

26. Foster, W. C., and Hausler, R. W.: Studies in Acute Intestinal Obstruction. II. Acute Strangulation, Arch. Int. Med. **34**:697 (July) 1924.

27. Hartwell, J. A.: Intestinal Obstruction, J. Exper. Med. **18**:139, 1913. Hartwell and Hoguet (footnote 17).

28. Howell, J.: Experimental Observations on the Cause of Death in Acute Intestinal Obstruction, Brit. M. J. **2**:1645, 1913.

29. Murphy, F. T., and Vincent, Beth: An Experimental Study on the Cause of Death in Intestinal Obstruction, Boston M. & S. J. **165**:684, 1911.

30. Reichel, P.: Zur Pathologie des Ileus und Pseudoileus, Deutsche Ztschr. f. Chir. **35**:495, 1892-1893.

31. Wilkie, D. P. D.: Experimental Observations on the Cause of Death in High Obstruction, Brit. M. J. **2**:1064, 1913.

32. Scholefield, B. G.: Acute Intestinal Obstruction: Experimental Evidence of the Absorption of Toxin from Obstructed Bowel, with a Critical Review of Various Methods of Treatment, Guy's Hosp. Rep. **77**:160, 1927.

33. Schönbauer, L.: Die Fermente in ihrer Beziehung zu gewissen Erkrankungen der Gallenblase und zum Ileus, Arch. f. klin. Chir. **130**:427, 1924.

2. Animals with strangulation show the following variations from the picture in simple obstruction: They do not become dehydrated, and the changes in the chemistry of the blood and urine are less marked. There is, however, usually a rise in the urea (Whipple and his co-workers,[24] Foster and Hausler,[26] Gatch, Trusler and Ayers [25]). Copher and Brooks [16] reported death in strangulation without blood changes. Nobody reported any changes in the blood chlorides or carbon dioxide.

Fact 7.—The intestinal content from above the obstruction, or from a closed loop or from a strangulated loop, after being prepared in one of any number of ways and injected into another animal (preferably intravenously) will cause the rapid death of that animal with a typical clinical and pathologic complex which is as follows:

Clinical:

(1) Vomiting.
(2) Tenesmus and bloody diarrhea.
(3) Dilatation of the pupils.
(4) Tremor, weakness of the hind legs.
(5) Pulse, weak and rapid.
(6) Death.

Blood:

(1) Coagulation reduced.
(2) Rapid rise of nonprotein nitrogen, mostly due to urea.

Urine:

(1) Increase in amount.[34]
(2) Slight trace of albumin.[34]
(3) Sharp rise in nonprotein nitrogen excretion.[34]

Pathologic Observations:

(1) Blood concentrated and clots slowly.
(2) Spleen, liver and pancreas engorged liver may be tense and friable.
(3) Splanchnic vessels very prominent.
(4) Stomach may be injected about the cardia.
(5) The greater part of the mucosa of the small intestine presents a red, velvety appearance. This starts at a definite line 1 cm. below the pylorus, is most marked in the duodenum and gradually fades out toward the terminal ileum.
(6) There is an effusion of blood-stained fluid into the lumen of the small intestine.

Albeck [35] was the first to describe the toxic qualities of this material. This has been almost universally observed since. The clinical and pathologic pictures are fully described by Ellis,[36] Murphy and Vincent,[29]

34. Whipple and Cooke: Proteose Intoxication and Injury to Body Proteins I-Metabolism of Fasting Dogs After Proteose Injections, J. Exper. Med. **25**:461, 1917.

35. Albeck, V.: Experimentelle und klinische Untersuchungen über die Todesursache bei Dünndarmstrangulation, Arch. f. klin. Chir. **45**:569, 1902.

36. Ellis, J. W.: Cause of Death in High Intestinal Obstruction, Ann. Surg. **75**:429, 1922.

Stone,[37] Whipple and his co-workers [7] and others. These facts are well established.

Fact 8.—The intestinal content of an animal that has died of toxic injection is also toxic when prepared and injected in a similar way. The clinical and pathologic picture is identical with that described under fact 7. This process can be repeated indefinitely, the toxin always being recoverable from the intestinal content of an animal that has died from its injection.

This fact has been established by Ellis [36] and by Sweet [38] on the basis of many experiments. Other workers have not studied it, but there are no conflicting opinions.

Fact 9.—The content of normal dogs during fasting is only slightly toxic when prepared in the same way.

There is some dissension on this point. Opinions vary all the way from claims that the normal content is absolutely innocuous to statements that it is more toxic than obstruction content.

Clairmont and Ranzi,[39] Davis and Stone,[40] Dragstedt, Dragstedt and co-workers,[41] Ellis,[36] Sugito [6] and Whipple and his co-workers [42] claimed that normal content is absolutely nontoxic if prepared and injected while it is still fresh.

Cybulski and Tarchanoff,[43] Davis,[44] Falloise [45] and Kukula [46] claimed that there is a slight but definite toxicity to the normal content.

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37. Stone, H. B.: The Toxic Agents Developed in the Course of Acute Intestinal Obstruction and Their Action, Surg. Gynec. Obst. **32**:415, 1921.

38. Sweet, J. E.: Intestinal Obstruction, Experimental Research, Internat. Clin. **1**:72 (30th ser.) 1920.

39. Clairmont, P., and Ranzi, E.: Zur Frage der Autointoxication bei Ileus, Arch. f. klin. Chir. **73**:696, 1904.

40. Davis, D. M., and Stone, H. B.: Studies on the Development of Toxicity in Intestinal Secretion, J. Exper. Med. **26**:687, 1917.

41. Dragstedt, L. R.; Dragstedt, C. A.; McClintock, J. T., and Chase, C. S.: Extirpation of the Duodenum, Am. J. Physiol. **46**:584, 1918. Dragstedt, L. R.; Moorhead, J. J., and Burcky, F. W.: The Nature of the Toxemia of Intestinal Obstruction: Preliminary Report, Proc. Soc. Exper. Biol. & Med. **14**:17, 1916-1917.

42. Whipple, G. H.; Stone, H. B., and Bernheim, B. M.: Intestinal Obstruction, J. Exper. Med. **17**:307, 1913.

43. Cybulski, N., and Tarchanoff, J.: A propos des poisons normaux de l'intestin, Arch. internat. de phys. **5**:257, 1907.

44. Davis, D. M.: Intestinal Obstruction: Formation and Absorption of Toxin, Bull. Johns Hopkins Hosp. **25**:33, 1914.

45. Falloise, A.: Les poisons normaux de l'intestin chez l'homme et les moyens de defense contre ces poisons, Arch. Internat. de physiol. **5**:159, 1907.

46. Kukula, O.: Untersuchungen über Autointoxicationen bei Darmocclusionen, Arch. f. klin. Chir. **63**:773, 1901.

Roger and Garnier;[47] Wangensteen and Chunn[48] asserted that the normal content is at least as toxic as contents after obstruction.

Braun and Boruttau[49] maintained that the normal content is more toxic than obstruction content.

In view of these statements gleaned from the literature, it was thought best to strike a mean and say that the normal content may be toxic.

Fact 10.—Large amounts of this toxin may be introduced into the lumen of the normal small intestine without untoward results.

This fact is universally accepted without dissension. It has been amply proved by Davis,[44] Schönbauer,[33] Stone,[37] Whipple and his co-workers,[50] and Wilkie.[51]

Fact 11.—Death in high obstruction, closed loops and strangulation can occur without bacterial infection of the peritoneum or blood stream.

That death was due to peritonitis was held to be the case by some of the earlier observers. Albarran and Caussade[52] felt that this was true. They claimed that if bacteria did not get through gross openings in the wall of the intestine they found their way through the intact structure with a resulting peritonitis. This has been emphatically and completely disproved. Buchbinder[53] and Helmberger and Martina[54] were among the first to disprove this contention. The permeability of the intestinal wall to bacteria will be discussed more fully.

Some of the early workers believed also that septicemia played a part in the picture. Wrzosek[55] fed nonvirulent organisms to dogs

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47. Roger, H., and Garnier, M.: Les poisons du tube digestif, Rev. de méd. **26**:953, 1906.

48. Wangensteen, O. H., and Chunn, S. S.: Studies in Intestinal Obstruction: I. A Comparison of the Toxicity of Normal and Obstructed Intestinal Content, Arch. Surg. **16**:606 (Feb.) 1928.

49. Braun, W., and Boruttau, H.: Experimental-kritische Untersuchungen über den Ileustod, Deutsche Ztschr. f. Chir. **96**:544, 1908.

50. Whipple, G. H.: Intoxication of Intestinal Obstruction, Contrib. Med. & Biol. Research, Sir W. Osler, New York **2**:1065, 1919. Whipple; Stone and Bernheim (footnote 42).

51. Wilkie (footnotes 31 and 19).

52. Albarran, J., and Caussade, G.: Étude expérimentale sur les obstructions intestinales aiguës, xiii Cong. int. de méd., Compt. rend., Paris (Sect. de path. gén. et expér.) **2**:583, 1900.

53. Buchbinder, H.: Experimentelle Untersuchungen am lebenden Thier- und Menschendarm, Deutsche Ztschr. f. klin. Chir. **55**:458, 1900.

54. Helmberger, A., and Martina, A.: Experimentelle Untersuchungen über die Durchgängigkeit des Darmes für Bacterien, Deutsche Ztschr. f. Chir. **74**:527, 1904.

55. Wrzosek, Adam: Experimentelle Beiträge zur Lehre von dem latenten Mikrobismus, Virchows Arch. f. path. Anat. **178**:82, 1904.

over long periods of time. At subsequent postmortem examination, they were able to isolate the same organisms from the viscera. They thus concluded that bacteria could enter the blood from the intestinal lumen. Borszesky and Genersich [56] claimed to recover colon bacilli from the blood in a large percentage of subjects dying from high obstruction. They therefore concluded that this was the cause of death. Later investigation has shown that this is apt to be a terminal event in any death. Also, many workers since have definitely proved, by repeated sterile cultures that such a bacterial invasion does not exist in acute intestinal obstruction. The most conclusive of this evidence is seen in the work of Hartwell, Hoguet and Beekman.[11]

A study of these facts immediately stimulates thought and gives rise to many questions that need answering. The answers, unfortunately, are not easily forthcoming. Most of them are still being sought.

QUESTIONS CONCERNING CAUSE OF DEATH IN HIGH OBSTRUCTION

Question 1.—Why is it that the higher the obstruction the more rapidly death occurs?

This is the most fundamental and far-reaching question. If it could be answered, the cause of death in high obstruction would be known. I shall not attempt to discuss it here, but will let the reader attempt to find an answer in the theories that are to be developed later.

Question 2.—What is the explanation of the clinical picture?

Vomiting may be explained by the presence of the obstruction. The intestinal content comes up because it cannot go down. Peristalsis forces the material against the barrier, and a return flow results in the center of the stream. The vomitus is really squeezed out through the only available exit, which is the mouth. There may also be a toxic factor in this vomiting which will be taken up in detail later.

Dehydration is the direct result of the vomiting. Hartwell [17] showed this clearly. Braun and Boruttau [49] emphasized the fact that the secretion produced by the normal intestine in twenty-four hours is equivalent to almost the entire amount of blood and lymph in the body. The reabsorption of this fluid is the only reason that the normal body is not continually and progressively dehydrated. If, then, this reabsorption is prevented by obstruction, it is easy to see why an extreme dehydration results.

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56. Borszesky, C., and von Genersich, A.: Beiträge zur Lokaldiagnose der inneren Darmokklusionen und zur Frage der Autointoxikation, Beitr. z. klin. Chir. **36**:448, 1902.

The tremors and weakness, the weak rapid pulse, the low blood pressure and the coma will be taken up in detail later. It does not seem as if they could be explained entirely on the grounds of dehydration.

Question 3.—Why does leukopenia occur?

No explanations have been offered for this phenomenon. It is, however, evidence against the probability of an infective process being the cause of death.

Question 4.—Why is the fibrin increased?

No explanation of this fact is forthcoming.

Question 5.—Why does high blood urea occur?

This phenomenon of high obstruction was first described by Tileston and Comfort [57] in 1914. Cooke, Rodenbaugh and Whipple [24] were the next to call attention to it. The latter workers also concluded that this rise was proportional to the seriousness of the symptoms.

Of course, whenever the blood urea increases, one immediately thinks of impaired kidney function. In this case it would have to be considerably impaired to cause the degree of apparent retention that is so often seen. The answer is that retention of urea does not occur, but rather a greatly increased formation. Haden and Orr [58] and Whipple, Cooke and Stearns [59] have conclusively demonstrated that the nitrogen excretion of the urine in cases of obstruction as measured in the twenty-four hour specimen is four or five times the normal amount. That there may be slight kidney damage was demonstrated by McQuarrie, Irvine and Whipple.[60] After careful investigation, they determined that the kidney function as measured by its ability to excrete phthalein, urea and sodium chloride was slightly but definitely decreased. The presence of albuminuria, an occasional cast and a slightly increased amount of creatinine may be taken as further evidence of slight damage. However, all those who claim that there is serious renal damage have to explain how such a compromised kidney can excrete four or five times the normal amount of urea.

The next most obvious explanation is dehydration and the resulting concentration of the blood. In the first place, the rise in urea often

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57. Tileston, W., and Comfort, C. W. Jr.: The Total Nonprotein Nitrogen of Urea of the Blood in Health and Disease as Estimated by Folin's Methods, Arch. Int. Med. **14**:620 (Nov.) 1914.

58. Haden, R. L., and Orr., T. G.: The Cause of Certain Acute Symptoms Following Gastro-Enterostomy, Bull. Johns Hopkins Hosp. **34**:26, 1923.

59. Whipple, G. H.; Cooke, J. V., and Stearns, T.: Proteose Intoxication and Injury of Body Protein: II. Metabolism of Dogs with Duodenal Obstruction and Isolated Loops, J. Exper. Med. **25**:479, 1917.

60. McQuarrie, I., and Whipple, G. H.: I. Renal Function Influenced by Intestinal Obstruction, J. Exper. Med. **29**:397, 1919.

amounts to a 1,000 per cent increase, whereas the concentration of the blood as measured by hematocrit readings does not indicate a change even worth considering in this comparison (White and Bridge [61]).

One is forced to the conclusion that urea is being formed to a great excess somewhere in the body. Urea is formed from the breaking up of amino-acids, which in turn come from a splitting of the protein molecule. From this one must further deduce that the high urea content in this case is an index of a rapid destruction of protein or amino-acids, so rapid in fact, that the kidney excretion cannot keep up with it even though it be working overtime.

Analogous conditions (i. e., high blood urea accompanied by high nitrogen excretion) are described as follows:

(1) Injection of toxins obtained from the lumen of the gut above an obstruction (Whipple and Cooke [62]).

(2) Simple laparotomy (Whipple, Cooke and Stearns [62]).

(3) Sterile abscess (Cooke and Whipple [62]).

(4) Pleuritis (Cooke and Whipple [62]).

(5) Pancreatitis (Cooke and Whipple [62]).

(6) Bilateral suprarenalectomy (Stewart and Rogoff [63]).

(7) Anaphylaxis (Weil [64]).

Also, a high blood urea without kidney impairment is described by Cooke and Whipple [62] in pneumonia and acute yellow atrophy.

Another interesting point which will be discussed more fully is the fact that if a dog suffering from high simple obstruction is given fluids, especially saline infusion, the urea immediately shows a marked decrease and may even reach normal even though the obstruction still exists. This will be discussed more fully later.

Question 6.—Why does all this destruction occur?

Whipple and his co-workers expressed the opinion that it is the result of the action of some toxic body on the tissues. They explained that this may be a rather nonspecific reaction since it is seen in so many different conditions. They offered an explanation of the fact that the administration of the fluid lowers the urea by asserting that it causes a dilution of the toxins with a resultant dimunition of their

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61. White, J. C., and Bridge, E. M.: Loss of Chloride and Water from the Tissues and Blood in Acute High Intestinal Obstruction, Boston M. & S. J. **196**: 893, 1927.

62. Cooke, J. V., and Whipple, G. H.: Proteose Intoxication: IV. Metabolism of Dogs with Sterile Abscess, Pancreatitis and Pleuritis, J. Exper. Med. **28**: 223, 1918.

63. Stewart, G. N., and Rogoff, J. M.: Studies on Adrenal Insufficiency, Proc. Soc. Exper. Biol. & Med. **22**:394, 1924.

64. Weil, R.: Studies in Anaphylaxis: XXI. Anaphylaxis in Dogs; A Study of the Liver in Shock and in Peptone Poisoning, J. Immunol. **2**:525, 1917.

activity. This theory, in substance, is concurred in by Haden and Orr,[58] McVicar [65] and Rabinowitch.[66]

Gamble and Ross [67] expressed the opinion that the high urea was the result of dehydration and impaired renal function. Brown, Eusterman, Hartman and Rowntree [12] thought that kidney impairment is the overwhelming factor. None of these workers, however, gives any reports on the excretion of urinary nitrogen, nor do they give details of the pathologic process discovered in the kidneys. This would seem important.

Hartmann and Smyth [67a] approached the problem from a slightly different angle. They suggested that the urea appears in the blood to compensate, in some rather obscure manner, for the loss of chloride. They inferred that it may have some action either in the acid-base mechanism or in keeping the osmotic relations in proper balance.

Bacon, Anslow and Eppler [68] mentioned the fact that there are rises in the urea in any condition calculated to cause dehydration. They killed dogs in a few hours by hypertonic saline infusion and the resultant dehydration. They noticed a rise in urea in these cases and attributed it to loss of water. They offered the following explanation: In dehydration, the water of hydration is removed from the protein molecule to make up for the deficiency. This may result in the disintegration of the protein molecule with an accompanying formation of urea. This theory sounds very well, but its application as a possible explanation of the high amount of urea in obstruction is weakened by the fact that they noticed a marked hyperpyrexia in all their cases. This, of course, does not occur in obstruction.

Question 7.—Why do the blood chlorides decrease?

MacCallum, Lintz, Vermilye, Leggett and Boas [69] first demonstrated low amounts of chlorides in their work on pyloric obstruction. From their researches they also showed a definite benefit derived from the administration of chloride.

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65. McVicar, C. S.: A Discussion of the Clinical and Laboratory Clinical Findings in Certain Cases of Obstruction in the Gastro-Intestinal Tract: The Rôle of Blood Chemistry in Diagnosis, Prognosis and Treatment of this Condition, Am. J. M. Sc. **169**:224, 1925.

66. Rabinowitch, I. M.: The Prognostic Value of the Study of the Blood Chemistry in the Acute Abdomen, Canad. M. Ass. J. **11**:163, 1921.

67. Gamble, J. L., and Ross, S. G.: The Factors in the Dehydration Following Pyloric Obstruction, J. Clin. Invest. **1**:403, 1925.

67a. Hartmann, A. F., and Smyth, F. S.: Chemical Changes in the Body Occurring as the Result of Vomiting, Am. J. Dis. Child. **32**:1 (July) 1926.

68. Bacon, D. K.; Anslow, R. E., and Eppler, H. H.: Intestinal Obstruction, Arch. Surg. **3**:641 (Nov.) 1921.

69. MacCallum, W. G.; Lintz, J.; Vermilye, H. N.; Leggett, T. H., and Boas, E.: The Effect of Pyloric Obstruction in Relation to Gastric Tetany, Bull. Johns Hopkins Hosp. **31**:1, 1920.

Haden and Orr [70] demonstrated that reduction of chlorides was a constant observation in all cases of simple high obstruction. They further brought out the following facts:

(1) Lowering of chlorides is the first change in the blood chemistry following simple high obstruction, coming before the rise in urea.

(2) The higher the obstruction, the more rapid the loss of chlorides.

(3) They were able to keep dogs with duodenal obstruction alive from twenty-one to twenty-eight days with the subcutaneous administration of 500 cc. of 0.9 per cent salt solution a day. (Death at the end of this period might easily be attributed to starvation.)

(4) As long as they kept the blood chlorides at a normal level by the administration of saline, the other blood changes did not occur.

(5) Dogs in which an attempt to make up the loss of fluid was made by the administration of solutions of dextrose or sodium bicarbonate, died more quickly than animals which were untreated.

(6) Animals did not derive any benefit from attempts to repair the loss of fluid by the administrations of potassium chloride, ammonium chloride, calcium chloride or magnesium chloride.

(7) Animals with obstruction in which no attempt was made to make up the loss of fluid, but in which the loss of chloride was made up by small amounts of concentrated sodium chloride solution (50 cc. 10 per cent sodium chloride per diem), lived from twenty-one to twenty-eight days and did not show toxemia or blood changes.

They applied this form of treatment to patients suffering from high obstruction and found that it probably prolonged life in some cases. In its clinical application, they advised the administration of 1 Gm. of

70. Haden and Orr (footnote 58); Chemical Changes in the Blood of the Dog After Intestinal Obstruction, J. Exper. Med. **37**:365, 1923; Chemical Changes in the Blood of the Dog After Pyloric Obstruction, ibid. **37**:377, 1923; The Effect of Sodium Chloride on the Chemical Changes in the Blood of the Dog After Pyloric and Intestinal Obstruction, ibid. **38**:55, 1923; Chemical Changes in the Blood of the Dog After Obstruction of the Esophagus and the Cardiac End of the Stomach, ibid. **38**:477, 1923; Chemical Changes in the Blood of Man After Acute Intestinal Obstruction, Surg. Gynec. Obst. **37**:465, 1923; The Effect of Inorganic Salts on the Chemical Changes in the Blood of the Dog After Obstruction of the Duodenum, J. Exper. Med. **39**:321, 1924; Use of Sodium Chloride in Treatment of Intestinal Obstruction, J. A. M. A. **82**:1515 (May 10) 1924; Obstruction of the Jejunum: Effect of Sodium Chloride on the Chemical Changes in the Blood of the Dog, Arch. Surg. **11**:859 (Dec.) 1925; Experimental High Intestinal Obstruction in the Monkey, J. Exper. Med. **41**:107, 1925; Distribution of Chlorides in the Blood of the Dog After Experimental Intestinal Obstruction, ibid. **41**:113, 1925; The Sodium Content of the Blood of the Dog After Experimental Intestinal Obstruction, ibid. **41**:119, 1925; Experimental Obstruction of the Jejunum: Effect of Sodium Chloride Injected into Lumen of Intestines Below Obstruction, ibid. **41**:707, 1925; Effect of Jejunostomy on Experimental Obstruction of the Jejunum of the Dog, ibid. **43**:483, 1926; Blood Fibrin in Upper Gastro-Intestinal Tract Obstruction, ibid. **45**:427, 1927; Excretion of Nitrogen After Upper Gastro-Intestinal Obstruction, ibid. **45**:433, 1927; Treatment of Toxemia of Intestinal Obstruction, Colorado Med. **21**:140, 1924.

sodium chloride per kilogram of body weight by infusion or hypodermoclysis of a 3 per cent solution as an initial dose. After that it should be administered as the occasion arises to keep the blood chlorides at a normal level. This stands as a definite clinical aid in the treatment of subjects with simple obstruction.

Foster and Hausler [71] brought up an interesting variation. They felt that the loss of chloride was apt to occur only in what they called the "critical period." This, they stated, corresponded to the healing period of intestinal wounds in experimental animals and lasted for four or five days after operation. In their experiments, they took great care to keep the blood chlorides at the proper level for the first five days after operation. Animals treated in this way survived for periods of three or four weeks even when chlorides or water were not administered after the critical period. This work was corroborated by Gatch, Trusler and Ayers.[25]

Hartwell and Hoguet [72] stumbled on the value of chloride therapy ten years before Haden and Orr started their investigations. They reported that they could keep dogs with high obstruction alive for three or four weeks by making up for the loss of fluid. In order to do this, they gave large amounts of physiologic sodium chloride solution. It did not occur to them that the sodium chloride was an important factor.

Haden and Orr [73] then tried to account for this loss of chlorides. They did quantitative tests on the urine and vomitus and decided that enough was not lost by these avenues. They then observed that loss of chloride and toxemia resulted in obstructed monkeys and rabbits.[73] Rabbits cannot vomit. Monkeys were not observed to vomit. Building their theory on this basis, they decided that the Cl ion (Cl^-) acted as a specific antibody on some toxin that was circulating in the blood as a result of the obstruction. They conceived of the reaction as being somewhat like this:

$$X\ (\text{Toxic}) + NaCl + H_2CO_3 = NaHCO_3 + X\ (HCl)\ (\text{nontoxic})$$

Thus, they believed, a large amount of chloride is held in the tissues. This toxin, they thought, caused a destruction of protein with the formation of urea. When the toxin was neutralized by administration of the chloride, the excess urea was excreted and no more was formed. There are two weaknesses in this theory, one of which they themselves

71. Foster, W. C., and Hausler, R. W.: Acute Intestinal Obstruction: III. Simple Obstruction, Arch. Int. Med. **36**:31 (July) 1925.

72. Hartwell, J. A., and Hoguet, J. P.: Experimental Intestinal Obstruction in Dogs with Especial Reference to the Cause of Death and the Treatment by Large Amounts of Normal Saline Solution, J. A. M. A. **59**:82 (July 13) 1912.

73. Haden and Orr (footnote 70, tenth reference).

discovered and failed to bring out, and the other of which they overlooked. In the first place, they showed that the administration of chlorides in forms other than sodium chloride did no good. In the second place, animals dying from high obstruction without vomiting have greatly dilated stomachs and upper intestines which are filled with large amounts of fluid.

However, in favor of their theory of a detoxifying action of chloride are the following observations:

Peabody [74] observed a fixation of the chlorides in the tissues in pneumonia.

Loeb (quoted from Hastings, Murray and Murray [75]) discovered that the toxicity for the adult *Fundulus* of sodium bromide, sodium sulphate and sodium nitrite was abolished by adding sodium chloride.

Sugito [6] reported that the toxicity of intestinal contents after obstruction was lost when the substance was dialyzed for several hours through a collodion sac against physiologic sodium chloride solution. He further reported that the toxin formed crystals with the chlorides of heavy metals.

Another interesting side-light is seen in the fact that Rackemann, Longcope and Peters [76] found low amounts of chlorides in serum sickness.

On the other hand, Copher and Brooks [23] and Gatch, Trusler and Ayers [25] and others pointed out that the administration of the chloride does not do any good in the treatment of strangulation. Furthermore, Copher and Brooks [23] did not find any loss of chlorides in animals dying from toxic injection. In addition, they mixed the toxic substance with sodium chloride and injected it without any diminution in its effect. They also could not demonstrate any beneficial effect if large amounts of sodium chloride were administered subcutaneously and intraperitoneally before and after toxic injection.

Gatch, Trusler and Ayers [25] made careful quantitative examination of the vomitus, urine, blood and tissues in cases of obstruction. They found that the tissue chlorides were reduced in the same proportion as the blood chlorides. They further found that there was enough loss of chloride in the urine and vomitus to account easily for this reduction. They observed the same thing to be true of the chloride content

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74. Peabody, F.: Studies of the Inorganic Metabolism in Pneumonia With Especial Reference to Calcium and Magnesium, J. Exper. Med. **17**:71, 1913.

75. Hastings, H. B.; Murray, C. D., and Murray, H. A.: Certain Chemical Changes in the Blood After Pyloric Obstruction in Dogs, J. Biol. Chem. **46**:223, 1921.

76. Rackemann, F. M.; Longcope, W. T., and Peters, J. P.: The Excretions of Chlorides and Water and the Renal Function in Serum Disease, Arch. Int. Med. **18**:496 (Oct.) 1916.

of the fluid in the stomach and upper intestine of animals that had died without vomiting. In addition, they observed low amounts of blood chlorides in animals that had both ureters ligated. In this condition, vomiting is a marked and frequent symptom. These observations have been confirmed in substance by Brown, Eusterman, Hartman and Rowntree,[12] Gamble and Ross,[67] Ingvaldsen, Whipple, Bauman and Smith,[8] and White and Bridge.[77]

Question 8.—Why does the carbon dioxide combining power of the blood increase?

As is well known, a disturbance in the carbon dioxide combining power of the blood is an indication of a disturbance of the acid-base regulating mechanism of the body. The carbonic acid concentration of the blood is the most easily regulated of all the factors concerned in this relationship. The acid forming elements in the normal blood are composed of the following factors in approximately the proportions stated: HCO^{-}_{3}, 20 per cent; Cl^{-}, 50 per cent; $HPO^{=}_{4}$, 3 per cent; $SO^{=}_{4}$, 1 per cent; organic acids, 1 per cent; unknown acid (probably protein), 25 per cent. These figures are only approximate. The amount of HCO^{-}_{3} is the most easily adjustable and is regulated through the respiration. Therefore, if for one reason or another there is a loss of acid forming radicals from the body, this loss is made up by a retention of carbon dioxide and a subsequent rise in the HCO^{-}_{3} which keeps the acidity of the blood at the proper level. It has already been demonstrated that there is a great loss of Cl^{-} from the body. Therefore, it seems safe to assume that the carbon dioxide combining power of the blood increases to compensate for this loss. If this loss of acid goes on so rapidly or to such an extent that the increase in HCO^{-}_{3} and other acid elements can not keep up with it, there is a resulting alkalosis. This is further borne out by the fact that many patients and experimental animals show symptoms akin to tetany, which, it has been frequently proved, results from alkalosis. These symptoms are hyperexcitability and tremor. This idea was first formulated by MacCallum, Lintz, Vermilye, Leggett and Boas[69] and offered as an explanation of gastric tetany. McCann and Hastings, Murray and Murray[75] were the first to demonstrate the high carbon dioxide combining power of the blood in obstruction. This is further concurred in by Brown, Eusterman, Hartman and Rowntree,[12] Gamble and Ross[67] and others.

Some even go so far as to suggest that this disturbance in the acid-base adjusting mechanism is the overwhelming factor in the toxic picture of high obstruction (Gamble and Ross,[67] White and Bridge[77]).

77. White, J. C., and Bridge, E. H.: Loss of Chloride and Water from the Tissues and Blood in Acute High Intestinal Obstruction, Boston M. & S. J. **196:** 893, 1927.

Portis and Portis [78] described an elaborate experiment whereby they produced an isolated loop of duodenum which they were able to wash out and drain at will. They demonstrated a marked loss of hydrochloric acid from the loop with the early development of the symptoms of tetany and death. They found that they could prevent this sequel, or stop it if it had already begun, by introducing 0.3 per cent hydrochloric acid into the loop in appropriate quantities. They forget, however, that a dog with a drained duodenal loop is apt to live indefinitely anyway.

Gamble and his co-workers [79] went a step farther. They studied the base-forming elements of the body which tend to offset the acid forming elements in maintaining the acidity of the blood at the proper equilibrium. They found them to be as follows in the approximate proportions indicated: Na^+, 90 per cent; Ca^{++}, 4 per cent; K^+, 3 per cent; Mg^{++}, 3 per cent. They emphasized the fact that there is no easy means of altering the base concentration as there is on the acid side. It is all relatively fixed. They concluded, therefore, that when base is lost, water must be lost at the same time in order to keep the base concentration at the proper level and maintain the acidity which is essential for life. They then investigated the various avenues by which base might be lost. They killed rabbits by producing high obstruction and examined the contents of their stomachs. Here they found a fluid which contained base, mostly in the form of sodium, chloride and water which represented losses equal to several times the initial total plasma content of each of these elements.

It seems, therefore, that the high carbon dioxide combining power is due to a loss of chloride and that the dehydration is due to a loss of water. Also, the fact that only water and sodium chloride combined does so much good is due in a large degree to the resulting addition of Na^+. If this is not added the animals will lose the fluid as fast as it is given to them. To explain the tendency to alkalosis, one must further assume that more Cl^- is lost than Na^+. If they were lost in equal amounts there would not be any disturbance of the acid-base ratio. Possibly the Cl^- is lost as hydrochloric acid and sodium chloride, while the Na^+ is only lost in the latter combination.

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78. Portis, M. M., and Portis, B.: Experimental High Obstruction, J. A. M. A. **85**:574 (Aug. 22) 1925.

79. Gamble, J. L.; Blackfan, K. D., and Hamilton, B.: A Study of the Diuretic Effect of Acid Producing Salts, J. Clin. Invest. **1**:359, 1925. Gamble, J. L., and McIver, M. A.: A Study of the Effects of Pyloric Obstruction in Rabbits, ibid. **1**:531, 1925. Gamble and Ross (footnote 67). Gamble, J. L.; Ross, G. S., and Tisdall, F. F.: The Metabolism of Fixed Base During Fasting, J. Biol. Chem. **57**: 633, 1923.

This contention of Gamble is further borne out in the experimental field by the following:

1. Gamble and Ross [67] were unable to prolong the lives of obstructed animals by making up the water loss with 5 per cent dextrose or ammonium chloride. All animals thus treated showed dehydration and the typical blood changes.

2. Haden and Orr [80] found the same result when they attempted to make up the loss of water with solutions of KCl, NH_4Cl, $CaCl_2$ or MgCl instead of NaCl.

3. Haden and Orr [81] found that dogs with obstruction in whom the loss of fluid was made up by distilled water died more quickly than if they were untreated.

4. Gatch, Trusler and Ayers [25] found that normal dogs without obstruction died in six days if they were given daily clyses of distilled water.

Before leaving this subject, it is well to state that all those who claim that death in high obstruction is due totally to dehydration and alkalosis, have to explain why death in closed loops and strangulation can intervene without any evidence of either phenomenon.

Question 9.—Why do urinary changes occur?

The urine is scanty as a result of dehydration.

The slight trace of albumin may be taken as an indication of slight kidney damage.

The increase in the nonprotein nitrogen excretion can be taken as the result of the excess amount circulating in the blood.

The low amount chloride excretion can be taken as an index of the decreased amount circulating in the blood.

The presence of phenol and indican suggests the fact that there may be some absorption from the intestine above the obstruction. These substances are products of protein putrefaction and are present in the intestinal content. Their presence in the urine was shown by Borszesky and Genersich [56] and Kukula.[46]

It should again be emphasized that there is no evidence of marked kidney damage.

Question 10.—Does the pathologic picture throw any light on the subject?

This question will be taken up and discussed in later connections. It is of but little assistance.

Question 11.—What deductions can one draw from the different pictures presented by simple obstruction, closed loops and strangulation?

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80. Haden and Orr (footnote 70, seventh reference).
81. Haden and Orr (footonote 70, fourth reference).

In view of what has already been discussed and from a careful comparison of the conditions, I think that one is justified in concluding that there are two conditions involved in intestinal obstruction in its broadest sense. These are: (1) Dehydration and an accompanying profound disturbance in the acid-base regulating mechanism; (2) an overwhelming toxemia.

If the problem is approached from this angle, one sees that the first process is most prominent in simple obstruction.

In experiments with closed loops both processes are at work at the same time to varying extents. If death occurs early, it is usually due to toxemia. If the animal survives for a while and vomits a good deal, dehydration and the accompanying disturbance in acid-base regulation again occur.

In strangulation, toxemia has the upper hand. The animal is overwhelmed and dies before he has a chance to become dehydrated.

The only change in the blood chemistry observed frequently in toxemia is an increase in the amount of urea.

The differences in these two conditions have been recognized by many workers (Foster and Hausler,[82] Gatch, Trusler and Ayers,[25] Hartwell and Hoguet,[72] Howell,[28] Murphy and Brooks,[16] and Wilkie [51]). Foster and Hausler [26] and Gatch, Trusler and Ayers [25] demonstrated the fact that the administration of water and sodium chloride was of no benefit in the treatment of strangulation. There are no conflicting opinions on this point.

If toxemia is present, what does it come from? The first answer that suggests itself is that it originates from the stagnating contents of the intestinal tract which have already been demonstrated to be highly toxic. The first man to suggest the possibility of toxic absorption from the intestinal tract was Amussat [83] in 1838. He treated a Monsieur Broussais who had carcinoma of the rectum which finally caused complete obstruction. He described the symptoms and downward course in great detail and suggested that death was due to absorption from the retained fecal matter. Bouchard,[84] in 1885, really sponsored the theory and was responsible for its great popularity. At one time physicians were inclined to ascribe all ills to toxic absorption from the intestinal tract. Gaspard (1822), Panum (1856), Hemmer (1866)

82. Foster and Hausler (footnote 26); Studies of Acute Intestinal Obstruction: I. Different Types of Obstruction Produced under Local Anesthesia, Arch. Int. Med. **34**:97 (July) 1924.

83. Amussat, J. Z.: La maladie de Broussais, suivie de quelques réflexions pratiques sur les obstructions du rectum, Épernay, 1845.

84. Bouchard, C.: Lectures on Auto-intoxication in Disease, Philadelphia, 1906, tr. French ed., 1887.

and Bergmann and Schmeideberg (1868) (quoted from Bouchard [84]) demonstrated that various products of putrefaction were highly toxic when injected into animals. Bouchard killed rabbits by injections of macerated muscle extract. He felt that there were four sources of intestinal auto-intoxication:

(1) Food.
(2) Bile.
(3) Putrefaction of alimentary residues.
(4) Fecal matter—mostly due to certain salts of potassium and ammonia.

Question 12.—What, then, is this toxic substance that is found in the intestinal content above an obstruction?

The answer to this question is not clear. The problem should be considered from different sides and then, if possible, conclusions reached.

One thing that should be borne in mind is that the toxin can be formed in a closed loop with almost unbelievable rapidity. Bunting and Jones [14] isolated it from the lumen of the bowel three hours after simple obstruction.

Question 13.—How must the content above an obstruction be prepared in order to demonstrate its toxic properties?

Murphy, Brooks and his co-workers [85] did not prepare it. They simply took the fluid content above an obstruction and used it for injections. Sometimes they strained it, and at other times they diluted it with an equal amount of distilled water.

Clairmont and Ranzi [39] filtered the contents through a Chamberland filter before injection.

Dragstedt, Dragstedt and co-workers [86] strained the fluid and heated it for one hour at 70 C. The coagulum was then filtered off, and the filtrate was kept with chloroform and toluene until needed for injection. Before using the substance, the preservatives were removed by heating and filtering.

Davis and Morgan [87] took the mucosa with the fluid. Then they mixed this with physiologic sodium chloride, added toluene and chloroform and allowed the mixture to autolyze at 37 C. for from two to ten

85. Copher and Brooks (footnote 23). Murphy and Brooks (footnote 16). Murphy and Vincent (footnote 29).

86. Dragstedt, C. A.; Dragstedt, L. R., and Chase.: The Antigenic Property of Closed Intestinal Loop Fluid, Am. J. Physiol. **46**:366, 1918.

87. Davis, D. M., and Morgan, H. S.: Natural Immunity of Animals Against Poison of Intestinal Obstruction, Bull. Johns Hopkins Hosp. **25**:39, 1914.

days. Before using the substance, they heated the mixture to 60 C. for thirty minutes and then centrifugalized and filtered it.

Whipple and his co-workers [88] heated the fresh contents to 60 C. for several hours. Then they centrifugalized and filtered the substance. Occasionally, they would allow it to autolyze with chloroform and toluene for several days.

Ellis [36] precipitated the substance with five volumes of 95 per cent alcohol. He extracted the precipitate with boiling water to which magnesium sulphate was added to salt out the protein. The subsequent filtrate was reprecipitated with five volumes of alcohol and then filtered. This precipitate, when dried, formed a fine white powder which he dissolved in water and dialyzed against distilled water (to remove the magnesium sulphate) before using. All these methods fully demonstrated a toxic property. The difficulty is in detoxifying it rather than in demonstrating its presence.

Question 14.—What are the chemical properties of this toxin?

There is not entire agreement concerning these properties, but from a survey of the literature, the following facts stand out:

(1) The toxin is held back by an earthen, but not by a paper, filter.[89]

(2) It does not pass through a collodion membrane.[90]

(3) It is not destroyed by boiling.[91]

(4) It is not destroyed by pancreatic digestion for seven days.[7]

(5) It is not destroyed by autolysis with intestinal mucosa for months.[92]

(6) It is not destroyed by erepsin.[36]

(7) It is probably destroyed by hydrolysis with 5 per cent sulphuric acid for six hours at 100 C.[7]

(8) Repeated precipitation removes its toxicity.[93]

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88. Stone; Bernheim and Whipple (footnote 7). Whipple; Cooke and Stearns (footnote 59).

89. Werelius, A.: Is Death in High Intestinal Obstruction Due to Liver Insufficiency? J. A. M. A. **79**:535 (Aug. 12) 1922.

90. Dragsted; Dragstedt and Chase (footnote 73). Whipple and Cooke (footnote 34). Whipple, G. H.; Rodenbaugh, F. H., and Kilgore, A. R.: V. Proteose Intoxication, J. Exper. Med. **23**:123, 1916.

91. Cannon, P. R.; Dragstedt, L. R., and Dragstedt, C. A.: Intestinal Obstruction: A Study of the Influence of the Bacterial Flora on the Toxemia of Acute Obstruction, J. Infect. Dis. **27**:139, 1920. Murphy and Brooks (footnote 16). Sugito (footnote 6). Whipple, G. H.: Intestinal Obstruction: A Proteose Intoxication, J. A. M. A. **65**:476 (Aug. 7) 1915.

92. Charrin and Le Play: Travaux originaux: Le rôle pathologique des poisons de l'intestin, Semaine méd. **24**:377, 1904. Whipple (footnote 91, fourth reference).

93. Whipple, G. H., and Van Slyke, D. D.: Proteose Intoxication and Injury to Body Protein: III. Toxic Protein Catabolism and its Influence on the Non-Protein Nitrogen of the Blood, J. Exper. Med. **28**:213, 1918.

(9) It loses its toxicity if dialyzed against physiologic sodium chloride for several hours.[6]

(10) It loses its toxicity by repeated filtration.[89]

(11) It loses its toxicity by long standing in the icebox.[89]

(12) It is soluble in water.[91]

(13) It is thrown out of solution rich in albumin by boiling.[92]

(14) It is precipitated by five volumes of alcohol.[93]

(15) It is precipitated by albumin.[6]

(16) It is precipitated by 60 per cent ammonium sulphate.[6]

(17) It does not stimulate pancreatic digestion.[94]

Question 15.—What substances have been demonstrated in the intestinal tract that might contain the toxic factor?

These substances might be divided into two classes: (1) those that are products of normal digestion plus normal bacterial action, and (2) those that are the products of stagnant digestion, where the bacterial action is more marked.

The substances produced by normal digestion plus normal bacterial action are as follows: From proteins—metaproteins, proteoses, heteroproteoses, deuteroproteoses, protoproteoses, peptones, polypeptids, amino-acids, ammonia, hydrogen sulphide, nitrogen, methyl mercaptan, phenol, cresol, dioxybenzene, phenylacetic acid, phenyl propionic acid, indol, skatol, tyrosine, dioxybenzene, resorcinol, hydroquinone and pyrocatechin[97]; from fats and lecithins—oxycholesterol, fatty acids, glycerol phosphoric acid, choline, neurine and muscarine[98]; from carbohydrates—derivatives of glucosamines and mucin, water, carbon dioxide and various disaccharids and polysaccharids.[99]

Stagnant digestion plus bacterial action, in addition to all of the forementioned substances, produces the following: Pyridine, chinoline, toxalbumins, ptomaines, diamines, tetramethylendiamine (putrescin), pentamethylendiamine (cadaverine), ethylendiamine and histamine.[44]

These products probably owe their existence to much increased bacterial action. From the foregoing list the following have a known

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94. Ellis (footnote 36). Whipple (footnote 91, fourth reference).

95. Whipple (footnote 91, fourth reference).

96. Ellis (footnote 36). Sugito (footnote 6). Werelius (footnote 89). Whipple (footnote 91, fourth reference).

97. Schloss, quoted by Gerard, R. W.: The Lethal Agent in Acute Intestinal Obstruction, J. A. M. A. **79**:1581 (Nov. 24) 1922. Kukula (footnote 46). Nesbitt, B.: On the Presence of Cholin and Neurin in the Intestinal Canal During its Complete Obstruction: A Research on Auto-Intoxication, Dominion M. Month. **12**:113, 1899. Sweet; Peet and Hendrix (footnote 22, second reference).

98. Gerard (footnote 97, first reference). Sweet; Peet and Hendrix (footnote 22, second reference).

99. Gerard (footnote 97, first reference).

toxicity: Proteoses, heteroproteoses, deuteroproteoses, protoproteoses, putrescin, cadaverine, histamine, choline, neurine and muscarine.[97]

Kukula [46] concluded that none of these existed in the intestine in sufficient quantities or were absorbed to a great enough extent to cause death.

It must be remembered that this is an extremely complicated field and that there probably exist in the intestine many substances that have not as yet been isolated.

Question 16.—What other substances does this toxic material resemble in its action?

In 1822, Gaspard (quoted from Bouchard [84]) found that if he injected extracts of putrid meat into experimental animals the resulting symptom complex and a pathologic picture were almost identical with those described for the injection of contents after obstruction. He is the first man to describe the hyperemia of the upper intestinal tract so characteristic of these conditions.

In 1856, Panum (quoted from Bouchard [84]) described the same thing. However, he took the precaution to boil his putrid extract before injection. He also found that the toxic factor could be precipitated by alcohol.

Whipple and co-workers [95] and Chittenden, Mendel and Henderson [100] brought out the striking similarity between the pharmacologic actions of the toxic substance and proteose as evidenced by marked fall in blood pressure, prolonged coagulation time and the increased flow and reduced coagulability of the lymph.

Stone [37] and Gerard [99] showed that the action of the toxin is almost identical with that of histamine.

Barger and Dale [101] described a symptom complex common to the pharmacologic actions of commercial peptone, extracts of intestines, thyroid, brain, etc., and of histamine which consists of vomiting, purging, salivation, labored respiration, low blood pressure, collapse and death. Histamine differs from the others in that it does not cause a loss of coagulation of the blood while the others do.

Whipple and his co-workers [102] brought out the similarity of the action of the toxin to the reactions seen in conjunction with large overdoses of epinephrine and fatal anaphylactic shock. South and Hardt [13] also emphasized the similarity of anaphylaxis. This will be taken up later.

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100. Chittenden, R. H.; Mendel, L. B., and Henderson, Y.: Chemico-Physiological Study of Certain Derivatives of the Proteids, Am. J. Physiol. **2**:142, 1898-1899.

101. Barger, G., and Dale, H. H.: β-Iminazolylethylamine, a Depressor Constituent of Intestinal Mucosa, J. Physiol. **41**:499, 1910-1911.

102. Whipple; Rodenbaugh and Kilgore (footnote 90, third reference).

Question 17.—What other conditions will cause the production of the toxin?

First of all, it has already been stated that the toxin can be recovered from the intestinal lumen of animals that have themselves been killed by toxic injection. Ellis [86] emphasized the fact that this makes its appearance with almost unbelievable rapidity. He produced a duodenal fistula in a dog and then subjected the animal to toxic injection. He collected duodenal contents before and after injection, and found that they almost immediately became toxic.

Gurd [103] found the intestinal contents toxic in a dog that had been killed by tying off the portal vein.

Magnus-Alsleben [104] described a strong toxicity of the intestinal content of dogs following a meat diet.

Ellis [86] described toxicity of the intestinal contents in dogs that have died from the following conditions: Thrombosed Eck fistula, distemper, acute pancreatitis, sterile peritonitis produced by dropping a piece of fresh pancreas into the abdominal cavity and bilateral suprarenalectomy.

Question 18.—What, then, is this toxin?

It has already been stated that it is not known what it is. The best that can be done is to quote the various opinions that have been expressed in the literature.

Whipple and his co-workers [105] thought that it is a proteose because it has the following properties in common with a proteose:

(1) Both are thrown out of a solution rich in albumin by boiling.
(2) Both are nondialyzable.
(3) Neither is destroyed by pancreatic digestion.
(4) Both are precipitated by alcohol and soluble in water.
(5) Both present the same clinical and pathologic picture when injected.
(6) Injection of both causes a rise of nonprotein nitrogen in the blood.
(7) Dogs are highly susceptible to both, while cats and rabbits are not.

However, dogs can not be immunized to toxic injection. Whipple and his co-workers performed a long series of experiments which seemed to show that dogs could be immunized to toxic injection and that by means of repeated sublethal doses of the toxin they could be made relatively immune to subsequent obstruction. However, although

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103. Gurd in Maury (footnote 1, first reference).

104. Magnus-Alsleben, E.: Ueber die Giftigkeit des normalen Darminhalts, Beiträge z. chem. Physiol. u. Path. **6**:503, 1904.

105. Stone, H. B.; Bernheim, B. M., and Whipple, G. K.: The Experimental Study of Intestinal Obstruction, Ann. Surg. **59**:714, 1914. Whipple (footnote 91, second reference). Whipple; Rodenbaugh and Kilgore (footnote 90, third reference).

their results look convincing, many other experimenters have tried and failed to show any signs of immunity (Brooks [20]; Dragstedt, Dragstedt and co-workers,[106] Davis and Morgan,[87] Ellis,[36] Magnus-Alsleben [104] and others). It seems as if Whipple's results along this line would have to be laid to normal variation.

Wilkie [19] also thought the substance a proteose.

Sweet,[107] Eisberg [5] and Schönbauer [108] ventured the opinion that it is a protein split product related in some way to the toxic proteoses. Sweet mentioned the possibility of the substance being attached to the proteose molecule rather than its being the proteose itself. This is borne out by the fact that the toxicity is lost by repeated filtration or precipitation.

Schönbauer [108] felt that it is a product of tryptic fermentation of albuminous decomposition products. He even went so far as to state that it is trypsin itself, which he believed is closely related in chemical composition to the protein split products. He reported the presence of trypsin in the peritoneum of dogs dying from high obstruction. He also reported beneficial results in high obstruction when injections of serum having a high antitryptic titer were given. He found the serum of diabetic persons to have this quality.

Stone [37] and Gerard [99] felt that it is histamine or a histamine-like product.

Wangensteen and Loucks,[109] working with histamine injections into the lumen of the bowel, could not obtain evidence of its absorption by normal, obstructed or distended gut.

Dragstedt, Dragstedt and co-workers [110] felt that it is related in some way to the toxic amines.

Eisberg and Draper [111] offered the suggestion that its is a substance of biochemical origin similar to parathyroid or other endocrine secretions.

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106. Cannon; Dragstedt and Dragstedt (footnote 91, first reference). Dragstedt; Dragstedt and Chase (footnote 73). Dragstedt, C. A., and Moorhead, J. J.: Immunity in Intestinal Obstruction, J. Exper. Med. **27**:359, 1918.

107. Sweet (footnote 22, first reference, and footnote 38).

108. Schönbauer (footnote 33). Schönbauer (footnote 33). Schönbauer, L., and Löffler, E.: Ueber Ileusserum: Experimentelle und klinische Untersuchungen, Wien. klin. Wchnschr. **38**:135, 1925.

109. Wangensteen, O. H., and Loucks, M.: Studies in Intestinal Obstruction: II. The Absorption of Histamine from the Obstructed Bowel, Arch. Surg. **16**: 1089 (May) 1928.

110. Dragstedt; Dragstedt, and Chase (footnote 86). Dragstedt; Dragstedt; McClintock, and Chase (footnote 15). Dragstedt and Moorhead (footnote 106, third reference).

111. Eisberg, H. B., and Draper, J. W.: Intestinal Obstruction: Continued Studies, J. A. M. A. **71**:1634 (Nov. 16) 1918.

Murphy and Vincent [29] and Williams [9] thought it is a bacterial exotoxin.

Nesbitt [112] thought that cholin is the toxic factor. Cholin has a curare-like action, increases intestinal movements and paralyzes the heart. This, of course, is not in accordance with the accepted picture of toxic injection. It does, however, suggest the possibility of there being more than one toxin as the cause of death.

Ingvaldsen, Whipple, Bauman and Smith [8] made a careful and delicate chemical analysis of the substance. After various purifying processes (which amplified the method used by Ellis [36]), they succeeded in isolating 1 Gm. of white powder from the combined contents of fourteen dogs with obstruction. They found that 71 mg. of this substance would kill a dog weighing 5.5 Kg., in two and three-quarters hours. After careful analysis of this substance, they decided that it was a nucleoprotein for the following reasons:

1. There was greater solubility in alkali and strong acids than in weak acids.

2. It was not coagulated by heat.

3. Chemical analyses and reactions showed that it contained phosphoric acid and a pentose.

They also demonstrated the presence of very small amounts of histamine in content obtained after obstruction. This, they felt, was not sufficient to cause symptoms.

Bouchard [84] thought it was an alkaloid.

Murphy and Brooks [16] suggested that it was a ptomaine.

I am afraid that I shall have to leave it to the reader to take his choice.

The next question to investigate is the possible origin of the toxin. Possibly some light can be thrown on the subject by investigating its source.

Question 19.—From what does the toxin come?

In investigating this question, it seems best to start at the beginning of the gastro-intestinal tract and to look into every possible source.

Question 20.—Is the toxin formed in the stomach?

The only evidence that the stomach is the elaborator of the toxin is found in the work of Roger and Garnier.[113] They isolated a toxic substance from the gastric mucosa which they called a gastrotoxin.

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112. Nesbitt (footnote 97, third reference).

113. Roger and Garnier (footnote 47); Note sur la toxicité des extraits préparés avec les parois du tube digestive, Compt. rend. Soc. de biol. **64**:426, 610 and 883, 1908.

This has not been confirmed by any subsequent observation. Ellis [36] found gastric contents nontoxic. Stone [37] felt that the toxin was not formed in the stomach. Many other workers agree. It looks as if Roger and Garnier's observations would again have to be attributed to normal variation. The general opinion is that the stomach is not the source.

Question 21.—Does the toxin come from the biliary tract?

Bouchard [84] reported that normal bile is toxic. However, it is easy technically to eliminate the excretion of bile from the gastro-intestinal tract and then produce obstruction in the animal, thus ruling out the bile. This experiment has been performed repeatedly by many workers who come to the universal conclusion that the elimination of the bile does not influence the picture (Bunting and Jones,[14] Draper Maury,[114] McClure,[115] Sweet,[116] Stone, Bernheim and Whipple,[7] and others).

Question 22.—Does the toxin come from the pancreas?

The idea of ascribing the origin of the toxin to the pancreas is an attractive one. In the first place, the clinical pictures of high obstruction and acute pancreatitis are almost identical (Sweet [117]). Then, the toxin can be recovered from the intestine of an animal that has died of acute pancreatitis (Ellis [36]). Also, the pancreatic juice is the chief protein splitter of the body and there are those that think the toxin is a protein split product. In addition to this, pancreatic juice is itself toxic when injected after being activated. And, finally, the lethal line of Draper lies just below the opening of its duct in the dog.

In considering the evidence of the toxicity of the pancreatic secretion, the outstanding example is acute pancreatitis in which, it is believed, the enzymes become activated, find access to the blood stream and cause sudden death.

Sugito [6] reported that normal pancreatic secretion is not toxic. He observed, however, a rapid development of a great toxicity if he added a small number of bacteria to it. Cybulski and Tarchanoff [43] reported a toxicity of pure pancreatic juice which, however, becomes greatly enhanced by putrefaction. They stated that its injection lowers the blood pressure, increases the rate of respiration and abolishes the

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114. Maury, J. W. D.: Intestinal Obstruction: An Outline for Treatment Based upon the Cause of Death, Am. J. M. Sc. **137**:725, 1909; (footnote 1, second reference).

115. McClure, R. D.: Experimental Study of Intestinal Obstruction, J. A. M. A. **49**:1003 (Sept. 21) 1907.

116. Sweet (footnote 22, first reference).

117. Sweet, J. E.: High Intestinal Obstruction, Post-Operative Ileus and Acute Pancreatitis, Penn. M. J. **16**:520, 1912-1913; (footnote 22).

coagulability of the blood. Schönbauer [33] showed that simultaneous introduction of trypsin and bacteria into the peritoneum caused rapid death, while twice the amount of trypsin or twice the number of bacteria alone does not have any effect on the control animals. Sweet and his co-workers [117] found that if they put pancreatic juice or dropped a piece of fresh pancreas into a low closed ileal loop (which is normally compatible with life indefinitely), the animal became toxic and quickly died with the typical picture of high obstruction.

Further evidence of the possibility that the pancreas is the originator of the toxic substance lies in the fact that animals with simple obstruction die with maximal rapidity if that obstruction is at a point just below the entrance of the pancreatic ducts (fact 1). This was observed by Draper Maury,[118] Eisberg [5] and Sweet.[119] Draper Maury,[118] Sugito [6] and Eisberg [5] reported that life is prolonged in obstruction if, by one means or another, the pancreatic secretion is made to enter the intestinal tract aboral to the obstruction. This conclusion was drawn from a large number of experiments. Sweet and his co-workers [22] reported that if the pancreas is removed and high obstruction perpetrated, death will come in seven or eight days as opposed to death in two or three days if obstruction is established without the removal of the pancreas. They also expressed the opinion that obstructed depancreatized animals die with a slightly different picture. Sweet also emphasized the great similarity of the symptom complexes and pathologic pictures presented by high obstruction, acute pancreatitis and bilateral suprarenalectomy. In line with this, Sweet and Pemberton [120] demonstrated that injections of suprarenal and pituitary extracts have an inhibitory action on the pancreatic secretion which is independent of changes in the blood pressure.

This work is pregnant with possibilities and stimulating to the imagination. Could it be possible that absorption of activated pancreatic juice is the cause of death? And that conditions for the activation and absorption can be produced in a number of ways (i.e., by obstruction, closed loops, strangulation, bilateral suprarenalectomy, etc.)? And then, is it not possible that the toxic substance is reexcreted into the intestinal lumen, for instance, into closed loops? This idea has been toyed with by Sweet,[117] Draper Maury [118] and Eisberg. Such a conception would also explain, possibly, the extreme rapidity with which the toxin is formed as observed by Bunting and Jones.[4]

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118. Maury (footnote 1, second reference).

119. Sweet (footnote 117, first reference).

120. Pemberton, R., and Sweet, J. E.: Further Studies on the Influence of the Ductless Glands on the Pancreas, Arch. Int. Med. **5**:466 (May) 1910.

On the other hand one cannot escape the fact that depancreatized animals with obstruction die just the same and with a picture not to be distinguished from that presented by normal animals with obstruction (Bunting and Jones,[14] Ellis[36] and Sweet[116]). Furthermore, Ingvaldsen, Whipple, Bauman and Smith[8] demonstrated the presence of the toxin in the gut of depancreatized animals that had died from obstruction.

Thus the idea that toxin comes from the pancreas must be relinquished.

Question 23.—Does the toxin come from the intestinal mucosa?

Experimentation along these lines is immediately faced by the great difficulty of eliminating the intestinal mucosa and its influences from the experimental animal. The intestinal secretion consists of:

(1) A purely mucoid secretion from the glands of Brunner in the duodenum.

(2) Succus entericus which is made up of the following components:

(*a*) Enterokinase, the activating factor for the proteolytic enzyme of the pancreatic juice, converting tripsinogen to trypsin.

(*b*) Erepsin, which acts on the proteoses and peptones, breaking them up to amino-acids during the process of absorption. Erepsin cannot be obtained from the lumen, but is in the cells. Erepsin is also reported to exist in the liver, kidney, pancreas and other tissues. This is an important enzyme.

(*c*) Enzymes which act on the carbohydrates, converting polysaccharids and disaccharids to dextrose.

(*d*) Nuclease, which works on nucleoproteins, splitting the nucleic acid to purine and pyrimidine bases.

(*e*) Secretin, which stimulates pancreatic secretion.

Whipple and his co-workers[121] are the great champions of the intestinal mucosa as the elaborator of the toxin. They found that extracts of the mucosa of animals with obstruction contained the same toxic properties as the intestinal contents. They conceived of the toxic substance as being elaborated in the mucosa cells, some being excreted into the lumen of the gut, some remaining in the cells, and the remainder being excreted into the circulation, causing the toxic symptoms and death. In their experiments they report a toxicity of the contents coming from isolated drained loops. Building on this foundation, they constructed their theory which, in substance is as follows: The mucosa cells, they claimed, depend for their normal action on the stimulus received from the normal passage of intestinal contents. They are stroked and bathed by it and in return they produce the secretions necessary for digestion. If this process is interrupted, as it is in a simple obstruction, they suggested that the action of the cells becomes

121. Stone; Bernheim, and Whipple (footnote 105, first reference, and footnote 42).

perverted and instead they produce a poisonous substance. Their technic in their fundamental experiment was, however, open to criticism. As was pointed out by Sweet,[22] they made many of their isolated drained loops by double ligature of the duodenum and gastro-enterostomy distal to the second ligature. This, therefore, did not eliminate the possibility of there being a functional obstruction above the first ligature in the stump of the duodenum. Therefore, they could not claim that the toxin was not formed in this stump and reexcreted into the drained loop. Also, it must not be forgotten that drained loops are frequently compatible with life, and that a toxicity can sometimes be demonstrated in normal intestinal content.

Draper and his co-workers,[122] after experiments on over 400 animals, concluded that the toxin is a normal product of the duodenum related to the gastrotoxins of Roger and Garnier.[47] This substance, they felt, is normally neutralized lower in the intestinal tract. When an obstruction intervenes, however, the toxin is not detoxified, but is absorbed unchanged and causes death. This would seem to explain the greater fatality of high obstruction, because if the obstruction were lower there would be varying degrees of detoxication and a resultant prolongation of life. Ellis[36] also concurred in this theory to a certain extent. Draper and his co-workers tried to develop this theory into a therapeutic advantage by feeding the jejunal and ileal mucosa of normal animals to animals with obstruction with the idea of detoxifying the fluid produced by the obstruction. At first they reported beneficial results, but were later forced to retract their statement.

Schönbauer[33] felt that trypsin is the offending substance and described its presence in the Brunner glands of the duodenum. He thought that it becomes activated and forms a protein split product which is absorbed and causes the toxic picture.

Bunting and Jones[14] thought that the toxin is formed in the duodenum.

Hartwell[123] suggested that it is elaborated by the injured mucosa.

Others have tried to eliminate the mucosa from the picture as follows:

Dragstedt and his co-workers[4] isolated segments of intestine and left them open in the peritoneal cavity with all nerves and vascular elements intact. These animals remained well. At a later date another

122. Maury (footnote 114, first reference; and footnote 1, second reference): Draper, J. W.: Experimental Intestinal Obstruction: Report of Further Physiologic, Cytologic and Chemical Studies, J. A. M. A. **57**:1338 (Oct. 21) 1911; footnote 10; Intestinal Obstruction, ibid. **67**:1080 (Oct. 7) 1916. Eisberg and Draper (footnote 111).

123. Hartwell (footnote 27, first reference).

laparotomy was done and the loop contents were found to be sterile. The ends were then inverted and the sterile closed loops were returned to the abdomen as before. They found that animals thus treated lived indefinitely regardless of from what level the loop was taken. They further were able to strangulate these loops without any deleterious effect to the animal. From this they concluded that the intestinal secretion could have nothing to do with the elaboration of the toxin.

Davis and Stone [40] found that normal intestinal secretion from which bacterial action had been eliminated by the addition of chloroform and toluene could be autolyzed indefinitely without becoming toxic. They claimed that this method did not stop enzyme action, and they therefore concluded that intestinal secretion did not form the toxin.

Gerard [90] called attention to the fact that the formation of toxin goes on in a strangulated loop, where the mucosa is largely rotted away. He offered this as evidence of the fact that intestinal mucosa cannot elaborate the toxin.

Murphy and Brooks [16] tied the cystic duct of dogs and found it compatible with life. They then inserted into the thus distended gallbladder a few loopfuls of culture obtained from the intestinal contents after obstruction. These animals quickly died of the typical picture of toxemia. From this they concluded that the intestinal mucosa is not at all necessary for the elaboration of the toxin.

Question 24.—Is, then, the toxin the result of bacterial action? This subject has already been touched on.

Those who have tried to ascertain the rôle played by bacteria are faced by the great difficulty of eliminating them entirely from the intestinal tract. The normal intestinal tract is inhabited by great quantities of bacteria of varieties too numerous to mention—aerobes and anaerobes. The most prominent aerobes are the members of the colon bacillus family while the Welch bacillus leads the list of the anaerobes. The normal small intestine is relatively sterile, especially in its upper reaches. The growth becomes more populous near the ileocecal valve, and is tremendous in the colon which is the happy hunting ground for bacteria. It is a well known fact that the intestinal content of any animal that has died from high obstruction, closed loop or strangulation is rich in bacteria no matter where the obstruction exists. What is the significance of this fact?

There is good evidence to prove that normal intestinal content, if incubated presumably to promote bacterial activity, will develop toxic properties in a relatively short time. This has been nicely proved by Davis and Stone,[40] Murphy and his co-workers [124] and Sugito.[6] Fur-

124. Murphy and Brooks (footnote 16). Murphy and Vincent (footnote 29).

thermore, Davis and Stone showed that normal contents do not develop toxicity as long as bacterial action is eliminated. Albu [125] and Bouchard [84] also thought that the toxin is the result of putrefaction, comparing the pharmacologic action to that of putrid meat.

On the other hand, Whipple and his co-workers [42] stated that normal mucosa extract putrefied and antolyzed did not produce toxicity. Roger and Garnier [126] also felt that putrefaction has little to do with it.

From the application of this to the experimental field, the following is found:

Zimmerman [127] reported two cases of infants born with congenital atresia of the small intestine. They died without showing signs of toxemia. He attributed this to the absence of organisms in their intestinal tract.

Albeck [35] did a very interesting experiment. He observed the fact that the intestinal tracts of hibernating animals are sterile. Therefore, he strangulated 20 cm. of the small intestine of a hibernating hedge hog. The animal did not wake up until the second day when it drank some milk. Death occurred on the sixth day. He was inclined to attribute the death to the fact that it introduced bacteria into its intestinal tract by drinking the milk and the resultant putrefaction.

Dragstedt, Dragstedt and co-workers [128] tried many methods of sterilizing a closed loop. They found that if they washed out the loop with ether before closing, a large proportion of dogs lived regardless of the level of the loop. At postmortem examination, however, they found bacteria in small numbers in these loops. They attributed this survival to some astringent action of the ether on the intestinal mucosa which reduced its permeability. They obtained the same results with tannic acid.

Their experiments by which they could sterilize loops by leaving them open in the peritoneal cavity have already been described. From these experiments, they concluded that health was not compromised in obstruction in the absence of bacteria, and that therefore microorganisms elaborated the toxin. Murphy and Brooks [16] did the same experiments with similar results. These workers took this to be final proof that bacteria elaborated the toxin and had, therefore, to be present

125. Albu, A.: Die Autointoxicationen des Intestinaltractus, Berlin, 1895, chapter 1, pp. 16-23.

126. Roger, H., and Garnier, M.: Nouvelles recherches sur les poisons intestinaux, Rev. de méd. **30**:233, 1910.

127. Zimmerman, H. B.: Acute Intestinal Ileus, Minnesota Med. **5**:156, 1922.

128. Dragstedt; Dragstedt; McClintock, and Chase (footnote 31, first reference; and footnote 15, first reference); Dragstedt and Moorhead (footnote 106, third reference). Dragstedt; Moorhead, and Burcky (footnote 41, second reference; and footnote 4).

in all cases of the toxemia of high obstruction. Largely as a result of this work, many other investigators were swung around to this opinion (Gerard,[99] Gurd,[129] South and Hardt,[13] Wilkie,[19] and others). Stone [87] claimed that histamine was formed by bacterial action and suggested that it was the cause of death.

If it is due to bacterial action, what bacteria are responsible? Clairmont and Ranzi,[29] after considerable experimentation, expressed the opinion that the aerobic bacteria, rather than the anaerobes, were responsible. Scholefield [32] favored the anaerobes, especially *B. welchii.*

Williams [9] did a careful and interesting piece of work on this subject. He quoted the report of the Committee on Anaerobic Bacteria which functioned during the World War. They give the following description of the toxemia associated with gas gangrene: "Vomiting is frequent. The pulse is rapid. The extremeties are cold and blue. The temperature falls. The mind stays acute to the end. In the terminal stages some degree of icterus may be present." He noticed the marked resemblance between this picture and that of toxemia in high obstruction. Therefore he studied the Welch bacillus as the elaborator of the toxin producing death.

He observed that the Welch bacillus was by far the commonest anaerobe in the intestinal tract. He isolated it from the vomitus and intestinal content after obstruction in a high percentage of cases of ileus.

He studied the conditions necessary for its growth and production of toxin. He found that it needed a neutral or slightly acid medium. This, he found, was provided in the small intestine, especially the terminal ileum. In the colon, where the medium is acid, he found but few living organisms of this species.

He next tried to prove that the toxic substance in intestinal material after obstruction was Welch bacillus toxin. Accordingly, he made injections into two series of mice, one with the contents after obstruction and the other with the contents plus Welch bacillus antitoxin. He found that in the first series of mice, 50 per cent died, whereas in the second they all lived. As further evidences of the absorption of Welch bacillus toxin, he noted fatty degeneration of the heart and liver and hemolytic staining of the intima of the arteries of patients dying from obstruction. This is also found in patients dying from gas gangrene. He stated that he was unable to demonstrate the presence of gas bubbles in the liver which, of course, is an outstanding feature in patients overwhelmed with gas bacillus infection, but is not an essential to his theory of toxin absorption from the intestine.

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129. Gurd, F. B.: The Toxins of Intestinal Obstruction, J. Infect. Dis. **15**:124, 1914.

He then applied the therapeutic test by treating patients suffering from acute appendicitis at St. Thomas' Hospital in London. He chose acute appendicitis, because it was fairly common, because the condition gives fair warning of various complications before these complications develop to the fullest extent, and because the mortality in the disease was well established (6.5 per cent at St. Thomas' Hospital). He gave the antitoxin in eighteen of 256 unselected cases in which, in the opinion of consultants, the chances of life were 50 per cent or worse. In this series, he had a mortality rate of 1.17 per cent. In a series of 111 control cases in the hospital at the same time, and in which antitoxin was not administered, the mortality rate was 6.3 per cent.

Also, in fifty-four cases of acute obstruction from one cause or another, he gave treatment in nineteen with five deaths. He quoted the mortality rate in these cases as being 9.3 per cent. He opposed this to 214 cases in the hospital from 1919 to 1923, in which treatment with antitoxin was not given, as being 24.8 per cent.

He reported an immediate and striking improvement in the patients as soon as they receive the treatment.

This seems rather convincing, but a closer study of the facts reveals certain weaknesses. In the first place, Welch bacillus toxin is extremely labile, being easily destroyed by heat and slight changes in acidity. The toxin generally conceded to be present in the obstruction material is stable, not even being touched by boiling. In the second place, it was unfortunate that he chose acute appendicitis for his therapeutic test, because there is an added factor of infection which might well be due in some degree to the Welch bacillus. Finally, his statistics on the treatment of pure high obstruction would be more convincing if he compared his percentage mortality in the cases in which treatment was given with the percentage mortalities in his control cases divided into groups of fifty-four consecutive admissions.

All those who claim that bacteria elaborate the toxin must answer the following questions:

1. Why is it that high obstruction is so much more fatal than low obstruction when the low small intestine contains many more bacteria than the upper? [130]

2. Why does the toxin appear so rapidly after obstruction? Bunting and Jones [14] reported its appearance in three hours after duodenal obstruction.

3. Why does the toxin reappear with such rapidity in the intestine of dogs that have received injections of it? Ellis [86] reported that it appears almost immediately.

130. Draper (footnote 122, fifth reference). Stone; Bernheim, and Whipple (footnote 7). Werelius (footnote 89).

4. Why does the toxin appear in cases in which there is no reason to suspect stagnation of intestinal contents? It is reported in acute pancreatitis, thrombosis of the portal vein, bilateral suprarenalectomy and distemper.[36]

Whipple and his co-workers [131] were unable to eliminate bacteria, but felt that they were ruled out for some of the foregoing reasons and also because with a closed washed loop there are symptoms which result in death, whereas postmortem examination shows very few organisms in the loop. Buchholz and Lange [132] were able to diminish the numbers of bacteria and completely avert their development by feeding acriflavine before obstruction. They reported that it did not influence the picture. Schönbauer [33] felt that bacteria were ruled out because strangulation of the colon is much less fatal than strangulation of the small intestine. Roger and Garnier [126] felt that putrefaction had little to do with the picture.

Question 25.—Does the toxin arise from partly digested food?

It is safe to assume that it does not arise solely from partly digested food. Most experimenters have taken the precaution of starving their animals before producing obstruction, thus eliminating this variable. There are, however, some interesting side-lights that suggest that food may increase the amount of toxin and cause its formation in normal gut. In the first place, it has already been demonstrated that certain products of normal digestion are toxic.

Roger and Garnier [133] found that the intestinal contents were nine times more toxic after a meat diet than after a milk diet.

Magnus-Alsleben [104] found the normal contents toxic after every kind of food but milk.

Wilkie [131] found that dogs died much more quickly from strangulation, if it was preceded by a protein diet.

Cannon, Dragstedt and Dragstedt [134] found proteolytic bacteria common in the intestinal tract, but were unable to eliminate them by any kind of diet.

This work would seem to add weight to the argument that the toxin is derived from protein digestion.

All the available evidence of the existence and formation of a toxin in the lumen of the obstructed intestine having been reviewed, the fol-

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131. Stone; Bernheim, and Whipple (footnote 7; footnote 105, first reference, and footnote 42).

132. Buchholz, W., and Lange, H.: Ileus and Darmflora, München med. Wchnschr. **74**:233, 1927.

133. Roger, H., and Garnier, M.: Influence du régime lacté sur la toxicité du content intestinal, Compt. rend. Soc. de biol. **59**:677, 1905; footnote 126.

134. Cannon; Dragstedt, and Dragstedt (footnote 91, first reference).

lowing question arises: Is this toxin the cause of the toxemia? Does it actually find its way into the circulation? If so, how?

Question 26.—Is this toxin the cause of the toxemia?

This question can best be answered by comparing the syndrome of injection with that of obstruction. In this, it seems best to compare strangulation with injection because in strangulation the toxemia is developed to the greatest extent. This data is given in the accompanying table.

Comparison of the Syndrome of Injection with Strangulation

	Strangulation	Injection
	Clinical	
Vomiting	+	+
Tenesmus	—	+
Diarrhea	—	+
Dilatation of pupil	No observation	+
Tremor, weakness in hind legs	+	+
Weak, rapid pulse	+	+
Low blood pressure	+	+
Death in coma	+	+
	Blood	
Leukopenia	+	No observation
Fibrin increased	+	No observation
Loss of coagulability	No observation	+
High urea	+	+
	Urine	
Amount	Scanty	Increased
Trace of albumin	+	+
High nonprotein nitrogen	+	+
Kidney function approximately normal	+	+
	Pathology	
Central nervous system normal	+	+
Lungs normal	+	+
Liver	Normal	Engorged
Spleen	Normal	Engorged
Pancreas	Normal	Engorged
Splanchnic dilatation	+	+
Stomach distended	+	—
Intestine distended	Above obstruction	—
Large amount of fluid in intestine	+	+
Intestinal mucosa injected	+	+

These comparisons have been found in different parts of the literature and it does not seem necessary to quote all the references. Whipple and his co-workers [135] go into this comparison more deeply than do any of the other authors. There truly is a marked resemblance. Possibly the differences can be explained by the fact that in one case there is mechanical obstruction and slower absorption, whereas in the other an overwhelming dose is given all at once.

Whether or not they resemble each other enough to be considered due to the same process is largely a matter of personal opinion.

135. Stone; Bernheim, and Whipple (footnote 7). Whipple and Cooke (footnote 34).

The majority of workers believe that they are the same picture (Dragstedt, Dragstedt and co-workers,[136] Stone,[37] Whipple and his co-workers [137] and many others).

Braun and Boruttau,[40] Foster and Hausler,[71] Hartwell and his co-workers,[11] South and Hardt [13] and Werelius [89] think that the two pictures do not bear enough similarity to be due to the same process.

Again, the reader will have to take his choice. Perhaps more light can be thrown on the subject by what follows.

Question 27.—What evidence is there that a toxin is absorbed?

In the first place, an animal may live for a long time with a closed loop which contains many times the lethal dose of toxin. This has been often proved (Dragstedt, Dragstedt and co-workers,[138] Murphy and Brooks,[16] Whipple and his co-workers [7] and others).

McLean and Andries,[139] Werelius [89] and Clairmont and Ranzi [39] tried transfusing the entire blood content from a toxic animal with obstruction into a normal animal. They did not obtain any toxic effect.

Whipple and his co-workers gave a dog a large enough dose of toxin to produce marked symptoms. In two hours they transfused his whole volume of blood into a normal animal, without an unfavorable effect. This would indicate that the toxin is taken up rapidly and held somewhere outside the blood stream. It further suggests that the fact that toxin cannot be demonstrated in the blood would not necessarily mean that it was not absorbed.

Murphy and Brooks [16] did the following interesting experiment: They placed a cannula in the thoracic duct of a dog and collected the lymph. They then isolated a loop of small intestine and injected into it toxic material from the intestinal content of a dog that had died from obstruction. This done, they increased the pressure within the closed loop by means of a column of water. They noticed that the lymph soon became bloody. The material, when injected, caused toxemia and death with the typical picture. Normal lymph, they found, was not toxic.

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136. Dragstedt; Dragstedt, and Chase (footnote 86). McClintock; Dragstedt, and Dragstedt (footnote 21).

137. Stone; Bernheim, and Whipple (footnote 7). Whipple and Cooke (footnote 34). Whipple, G. H.; Stone, H. B., and Bernheim, B. M.: Intestinal Obstruction: A Study of a Toxic Substance Produced in Closed Duodenal Loops, J. Exper. Med. **17**:286, 1913.

138. Dragstedt; Dragstedt; McClintock, and Chase (footnote 15, first reference).

139. McLean, A., and Andries, R. C.: Ileus Considered Experimentally, J. A. M. A. **59**:1614 (Nov. 2) 1912.

140. Sauerbruch, F., and Heyde, M.: Weitere Mittheilungen über die Parabiose bei Warmblütern mit Versuchen über Ileus und Urämie, Ztschr. f. exper. Path. u. Therap. **6**:33, 1909.

Sauerbruch and Heyde [140] experimented with animals living in parabiosis. They found that when one was obstructed they both showed symptoms. If they were then separated, the one that was not obstructed recovered.

Sugito [6] produced closed loops in dogs. During the last moments of life, he aspirated blood from the veins in the mesentery coming from the loop. He then separated the serum from this blood and injected it into mice. He found that it killed them in from three to fourteen hours. He found that serum from the mesenteric veins of normal animals was nontoxic. Scholefield [32] corroborated these observations of Sugito and emphasized the fact that the blood must be obtained during the last moments of life to show toxicity.

Sugito [6] claimed that the toxin could be isolated from the blood of animals with obstruction by tryptic digestion of serum albumin.

Schloss [99] reported a histamine-like body which he recovered from the blood of infants suffering from obstruction.

There is then some evidence of a toxin circulating in the blood. If the toxin does get into the blood, what possible channels of entrance are there?

Question 28.—Does toxin get in through the intestinal mucosa?

It has been amply proved that the normal intestinal mucosa is impervious to the toxin (fact 10), but the mucosa above an obstruction cannot be called normal. It nearly always shows gross changes, and there is no reason to believe that, even in the absence of any gross or histologic changes, its physiology is not profoundly affected. In studying the absorptive properties of the intestine above an obstruction, the presence of indican and phenol in the urine (Kukula [46]) may be taken as evidence of absorption from the obstructed gut.

Braun and Boruttau [49] injected strychnine into the lumen of normal gut in quantities varying from 1.2 to 3 mg. Cramps began in five and one-half minutes, and death in thirteen and one-half minutes. In animals with obstruction which received like doses they observed the onset of cramps in between ten and fifteen minutes and death supervened in from twelve and one-half to thirty-five minutes. They took this as proof of the fact that absorption was present but lessened in obstructed gut.

Clairmont and Ranzi [39] injected calcium iodide (205 cc. of a 2 per cent solution) into the lumen of the gut and then tested the urine at frequent intervals for the presence of iodine. In this way they constructed curves for normal and obstructed animals which they took to be indices of the absorption of this element. After many experiments they determined that the absorption above an obstruction was more than normal at first, reaching a peak at about the end of the first half of the survival period. After that it rapidly fell below normal.

Enderlen and Hotz [141] studied the absorption of sodium chloride and dextrose in 5 per cent solutions. They found that normally the substances were absorbed in quantities proportional to the fluid absorbed. In simple obstruction, they found the absorption much decreased and much excess of fluid secreted into the lumen. They also found absorption much decreased in closed loops.

Davis [44] found phenolsulphonphthalein actively absorbed by closed loops as tested by its excretion in the urine.

Falloise [45] injected the toxin into the lumen of gut, the mucosa of which had been damaged by sodium fluoride or hot water. He noted toxic symptoms.

Hartwell and his co-workers [142] were the first to bring out the theory that the toxemia did not make its appearance in the presence of uninjured mucosa. They recognized the great difference between simple obstruction and strangulation and attributed it to this. They searched all the protocols of Whipple and his co-workers and found that in every case in which death supervened with obstruction or closed loop, there were gross changes in the mucosa. They even carried it so far as to state that when obstruction or closed loop was caused by section and inversion, the element of injury to the mucosa was automatically introduced by the surgical procedure. They then devised a clamp with which to cause obstruction without compromising the circulation of the compressed gut. They claimed that dogs thus obstructed died only from starvation provided their water balance was maintained. They later modified this view and decided that damage done by section was immaterial.

Brooks and his co-workers [143] believed absorption through the injured mucosa was the most important factor in the production of the toxemia. They agreed with Hartwell that the toxemia is directly proportional to injury to the mucosa. They believed that this injury is caused largely by distention of the gut and the resultant compromising of the circulation. They called attention to the fact that the upper intestine is largely secretory in function, while the lower is largely absorptive. Thus in upper intestinal obstruction, the distention and resultant damage to mucosa makes its appearance much more rapidly than in lower intestinal obstruction. In this way they explained the extreme toxicity of strangulation and the fact that long closed loops are less rapidly fatal than short ones in which distention appears more

141. Enderlen and Hotz: Ueber die Resorption bei Ileus und Peritonitis, Mitt. a. d. Grenzgeb. der Med. u. Chir. **23**:755, 1911.

142. Hartwell (footnote 27, first reference). Hartwell and Hoguet (footnotes 17 and 72). Hartwell; Hoguet, and Beekman (footnote 11).

143. Brooks; Schumacher and Wattenburg (footnote 20). Copher and Brooks (footnote 23). Murphy and Vincent (footnote 29).

rapidly due to their very shortness. They feel that they proved the permeability of injured mucosa to the toxin by their experiment with a cannula in the thoracic duct which has already been described. They connect this theory with their theory of the bacterial origin of the toxin and state that there are two factors in the production of the toxemia of obstruction: (1) the elaboration of the toxin, which is the result of bacterial action, and (2) the absorption of the toxin which is proportional to injury to the mucosa. Of these two factors, they feel absorption to be by far the most important. In this way they feel that they have explained how the toxin can be of bacterial origin and still cause death more rapidly in obstruction in the upper reaches of the intestinal tract.

Stone and Firor [144] felt that high intra-intestinal pressure was the cause of the absorption of the toxic substance. They found that the normal intra-intestinal pressure was 1.5 cm. of water whereas the pressure above obstruction was over 150 cm. of water. They then tested the absorption of india ink from the normal intestine and found there was none. However, when they placed the substance in the lumen of the gut above an obstruction, they recovered it from the mesenteric glands and lymphatics. They then excised a loop of normal intestine, filled it with the toxic substance and placed it in Ringer's solution. They found that if they then inflated the loop with air, the Ringer's solution rapidly became toxic as tested by injection into an animal. This experiment does not, however, rule out damage to the mucosa.

This theory of absorption, as stated most clearly by Brooks and his co-workers, is held by many other investigators (Scholefield,[32] Gatch, Trusler and Ayers,[25] Wilkie,[19] Dragtedt, Dragstedt and co-workers,[145] Foster and Hausler,[71] Eisberg [5] and others). Van Beuren [146] found that in experimental simple obstruction the lesions of the mucosa usually first appeared at the end of forty-eight hours. He suggested that the toxemia begins at this time, and compares it with the well known clinical fact that in cases of obstruction surgical intervention is of little aid after the obstruction has persisted for over forty-eight hours.

I find but few opinions which oppose the theory that toxic absorption occurs through injured mucosa. The outstanding one is that of Whipple and his co-workers, whose theory has already been discussed in detail.

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144. Stone, H. B., and Firor, W. M.: Absorption in Intestinal Obstruction: Intraintestinal Pressure as a Factor, Tr. South. Surg. & Gynec. Ass. **37**:173, 1924.

145. Dragstedt; Dragstedt; McClintock, and Chase (footnote 15). Dragstedt; Moorhead, and Burky (footnote 41, second reference). McClintock; Dragstedt and Dragstedt (footnote 21).

146. Van Beuren, F. T., Jr.: Relation Between Intestinal Damage and Delayed Operation in Acute Mechanical Ileus, Ann. Surg. **72**:610, 1920.

The probability of the toxins being absorbed is accepted by the great majority of investigators. There is good proof that such is the case. On the other hand, it is difficult to imagine how toxin can be absorbed through the vascular elements of the mesentery in cases of strangulation in which at least the venous return is cut off and often the entire circulation is blocked. It should again be emphasized that death can occur in strangulation without peritoneal infection.

Question 29.—Is, then, the toxin absorbed by the peritoneum after passage through the intestinal wall?

The work of Stone and Firor [144] already described, in which they demonstrated toxicity of Ringer's solution which had contained an inflated closed loop of intestine filled with toxin would suggest this.

Braeye [147] held the theory that the intestinal wall was in some respects similar to a semipermeable membrane and would therefore conform to the laws of diffusion and osmosis. He quoted recent work which showed that a collodion membrane, impermeable to hemoglobin, could be made permeable by adding sodium oleinate and sodium glycocholate to the mixture. He therefore put an excised closed loop, full of toxin, into Ringer's solution and added 1 per cent soap solution. He was not able to demonstrate toxicity of the Ringer's solution.

Foster and Hausler,[26] working on this theory, put a strangulated loop in a rubber bag in an attempt to eliminate peritoneal absorption. They were not able to demonstrate any difference in the outcome.

The work of Schönbauer [33] deserves special consideration. He observed that a strangulated inguinal hernia was not nearly as fatal as a strangulated internal hernia. He ascribed this to the surroundings of the strangulated loop. He carried out the following experiments along this line:

Schönbauer put calcium iodide in the stomachs of normal animals by means of a stomach tube. He was unable to demonstrate any signs of absorption over a period of twelve hours as indicated by frequent examinations of the blood and urine, nor was he able to demonstrate any evidence of the substance in the peritoneal cavities of these animals.

He next repeated these experiments, except that after placing the calcium iodide in the stomach, he subjected the animal to a normal exploratory laparotomy. After this procedure, he found traces of the substance in the blood in six hours and large amounts in the peritoneal cavity at subsequent postmortem examination.

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147. Braeye, L.: Contribution to the Study of Toxic Absorption from the Intestinal Tract in Experimental High Obstruction, Bull. Johns Hopkins Hosp. **40**:33, 1927.

He made the following experiment to test whether the blood or the peritoneum received the substance first: After placing the calcium iodide in the stomach, he performed a laparotomy and washed the peritoneal cavity out with silver acetate, leaving some free in the abdomen at closure. In six hours, the dogs were very ill. He was unable to find any calcium iodide in the blood or urine, but on opening the peritoneal cavity he found a large precipitation of silver iodide and free calcium iodide.

He obtained the same results when similar methods were applied to simple obstruction and strangulation. Then he tested in a similar way the diffusion of various other substances through the intestinal wall. He found that crystalloids passed through more rapidly then colloids, and that bacteria did not pass through.

His experimentation is a great argument in favor of the most careful handling of intestines at operation.

Thus evidence shows that it is possible for substances to pass through the wall of compromised gut and be absorbed by normal peritoneum.

All the avenues of absorption having been considered, there is one remaining possibility by means of which the toxin can reach the circulation.

Question 30.—Is the toxin rather formed by the cells of the mucosa and secreted in both directions (i.e., into the intestinal lumen and into the blood stream)?

Many of the end-products of digestion are actually passed through the cells of the intestinal mucosa and these same cells secrete certain substances into the intestinal lumen. This theory is not so improbable as may at first seem. It is further attractive to the imagination because a similar phenomenon occurs in acute pancreatitis.

Whipple and his co-workers [148] were the chief advocates of this theory. It does not seem necessary again to describe their work.

Ellis [86] was also attracted by this theory, although he admitted the difficulty of proof. He made the suggestion that the bacteria may activate the mucosa cells to form the toxin.

Davis [44] at one time was inclined to favor this theory. He thought the normal contents were toxic in the upper intestine where there are no bacteria, and that a perverted action of the mucosa would cause the injection of this substance into the blood stream. He arrived at this rather by the process of elimination.

The subject of the toxin has been discussed from all possible angles. It seems as if the majority of the evidence would point to the fact that

148. Stone; Bernheim, and Whipple (footnote 105, first reference; footnote 42; Intestinal Obstruction: IV. Mechanism of Absorption from Mucosa of Closed Duodenal Loops, J. Exper. Med. **19**:166, 1914). Whipple (footnote 50, first reference).

it is elaborated in the intestine or mucosa, and finds its way, by one or more of a number of devious passages, to the circulation. By means of the circulation, it is carried to the various parts af the body, bringing with it destruction and death.

Question 31.—Does the toxin act on the central nervous system?

There is nothing in the pathologic picture which points to any actual destruction of nervous tissue; however, some observers have remarked concerning certain nervous manifestations.

Clairmont and Ranzi [39] observed symptoms mostly of a nervous character. They added brain substance to the toxin before injection and claimed to demonstrate a lessened toxicity. They further injected brain extract from a dog which had died from obstruction, and found that it killed a mouse in two days.

Magnus-Alsleben [104] isolated a substance from the upper intestinal tract of dogs. When this substance was injected into rabbits in small amounts, it caused general central paralysis, cramps and death due to respiratory stoppage.

Falloise [45] injected extract of feces and obtained a fall in blood pressure, dyspnea, clonic and tonic convulsions, exophthalmia and dilatation of the pupils.

Nesbitt [112] thought the toxic substance was choline, which is a powerful nerve poison.

Sugito [6] reported that he isolated the toxin from the brain of animals dying from obstruction. This substance, he states, is especially plentiful in the medulla.

Question 32.—Does the toxin act on the heart and large vessels?

There is no evidence of any action of the toxin on the heart and large vessels.

Question 33.—Does the toxin act on the lungs?

There is no evidence of any action of the toxin on the lungs

Question 34.—Does the toxin act on the liver?

The liver has received attention because, if the toxin is absorbed through the portal system it is the first organ to be affected.

Hartwell and Hoguet [17] described fatty changes in the liver at postmortem examination and compared them to those found in the toxemias of starvation, pregnancy, delayed chloroform poisoning and acute infections. Draper [10] and others could not find such changes.

Colp and Louria [149] emphasized the fact that increased blood urea is not seen in liver insufficiency. They were unable to find any marked changes in liver function as demonstrated by the phenoltetrachlorphthalein test.

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149. Colp, R., and Louria, H. W.: Liver Function in Intestinal Obstruction, Arch. Surg. **10**:756 (March) 1925.

Draper and Schultz [150] quoted Pohl in affirming that conjugation of camphor and glycuronic acid takes place in the liver. They thought that they demonstrated a slight reduction of liver function by this test.

Question 35.—Does the toxin act on the other splanchnic organs?

There is evidence of marked effect on the splanchnic organs, as shown by vomiting, bloody diarrhea, tenesmus, splanchnic congestion, engorgement of the liver, spleen and pancreas, and injection and ulceration of the intestinal mucosa. Whether this is due to direct or reflex action is not clear.

Question 36.—Does the toxin act on the kidneys?

There are signs of slight renal damage as evidenced by albuminuria, occasional casts, slightly reduced ability to excrete urea and sodium chloride.[60] This has already been discussed in detail.

Question 37.—Does the toxin act on all the cells of the body?

There is good evidence that the toxin produces rapid breakdown of protein molecules. This is indicated by the extreme and rapid rise in the urea in both blood and urine. This, too, has been discussed in detail.

Question 38.—Does the toxin act on the glands of internal secretion?

There is a certain strange and peculiar similarity between dogs that have died from toxic injection and those which have died after bilateral suprarenalectomy.

This was first noticed by Sweet [151] and Ellis.[36] They found that dogs died after bilateral suprarenalectomy with a picture indistinguishable from that following toxic injection. What is more, they were able to recover a similar toxin from the intestinal tracts of dogs dying from the former condition.

Stewart and Rogoff [152] described the following striking symptoms observed in suprarenalectomized dogs:

(1) Vomiting.
(2) Bloody diarrhea.
(3) Tremors, weakness and convulsions.
(4) Temperature normal or subnormal.

At postmortem examination, Stewart and Rogoff described the following observations:

(1) Deep injection and frequent ulceration of the entire gastro-intestinal tract, most in the duodenum.

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150. Draper, J. W., and Schlutz, F. W.: Glycuronic Acid Determination (Tollens) in Duodenal Obstruction, Proc. Soc. Exper. Biol. & Med. **9**:28, 1911-1912.

151. Sweet (footnote 117, first reference).

152. Stewart and Rogoff (footnote 63); Studies on Adrenal Insufficiency in Dogs: I. Control Animals not Subjected to Any Treatment, Am. J. Physiol. **78**: 683, 1926.

(2) Bloody exudate in the lumen of the gut.
(3) Congestion of the pancreas.

From the blood chemistry they note the following:

(1) Marked rise in the urea.
(2) Slight fall in the chlorides.

Sweet and Pemberton [120] noted an inhibitory action of suprarenal extract on pancreatic secretion regardless of changes in blood pressure.

Sweet [116] suggests epinephrine as a treatment for the toxemia of obstruction.

Of what significance is this similarity?

Another interesting and similar condition is anaphylaxis.

Question 39.—Is the toxemia in any way similar to an anaphylactic phenomenon?

This subject has already been mentioned in relation to the closely allied condition, protein intoxication.

A number of workers have remarked on the close similarity of toxic injection and anaphylactic shock in dogs (Whipple and his co-workers,[153] Sweet,[38] South and Hardt [13]).

Louria [154] described urticaria in a case of high obstruction.

Rackemann, Longcope and Peters [76] described low amounts of blood chlorides in serum sickness.

The following description of the picture of anaphylaxis in dogs is found in the combined works of Hisanobu,[155] Major,[156] Webb,[157] and Weil.[64]

Symptoms:

(1) Vomiting.
(2) Staggering gait, weakness in hind legs.
(3) Collapse, tremor.
(4) Low blood pressure.
(5) Weak, rapid pulse.

Pathology:

(1) Intense congestion and hemorrhage of the gastro-intestinal tract.
(2) Lungs, pleura and endocardium congested.
(3) Congestion of liver.

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153. Stone; Bernheim, and Whipple (footnote 7). Whipple; Rodenbaugh, and Kilgore (footnote 90, third reference).

154. Louria, H. W.: The Blood Urea Nitrogen in Acute Intestinal Obstruction, Arch. Int. Med. **27**:620 (May) 1921.

155. Hisanobu, K.: On the Distribution of the Non-Protein Nitrogen in Cases of Anaphylaxis and Peptone Poisoning, Am. J. Physiol. **50**:357, 1919.

156. Major, R. H.: Blood Chemistry in Allergy, Bull. Johns Hopkins Hosp. **34**:104, 1923.

157. Webb: The Mechanism of Anaphylactic Leucopenia in Dogs, J. Path. & Bacteriol. **27**:79, 1924.

Blood:

(1) Leukopenia.

(2) High nonprotein nitrogen, chiefly due to urea.

(3) Rise in creatinine.

(4) Fall in chlorides.

Flashman [158] reported that bilateral suprarenalectomy in rats increases their susceptibility to anaphylactic shock.

This provides more food for thought.

Question 40.—Finally, is there no toxemia and is death rather physiologic in character, being due to lack of some substance or substances necessary for life, or to nervous shock?

The theory of shock or a shock-like condition has attracted a few observers as a possible cause of death in strangulation.

Braun and Boruttau [49] expressed the opinion that the nervous impulse due to occlusion not only has a mechanical action on peristalsis, but increases secretion to a great extent. This, they think, leads to such a diminution of circulatory fluid that the animal dies of inanition, comparable to death by exsanguination. They took kymographic records of animals dying in both conditions and found a great similarity.

McLean and Andries [139] propounded a somewhat similar theory. Being unable to demonstrate any toxic material, they felt that death was due to a depletion of the vascular and lymph systems causing grave disturbance of circulation, especially cerebral. They thought that a loss of sympathetic control played a large part in this phenomenon.

Foster and Hausler [159] felt that shock plays a large part in strangulation. They thought that a long loop is more rapidly fatal than a short one. They used this in building up their theory, saying that the shock is due to pain, glandular inactivity and loss of blood into the strangulated bowel. They felt that toxic absorption is practically a negligible factor, emphasizing the fact that nothing can be absorbed from a strangulated loop due to interference with the circulation. They thought that they had eliminated peritoneal absorption; then death resulted from a strangulated loop that had been placed in a rubber bag. Van Beuren,[160] von Khantz [161] and Wilkie [51] also thought that shock plays an important rôle.

158. Flashman, D. H.: Effect of Suprarenalectomy on Active Anaphylactic Shock in the White Rat, J. Infect. Dis. **38**:461, 1926.

159. Gamble; Blackfan, and Hamilton (footnote 8, first reference). Foster and Hausler (footnote 82, second reference).

160. Van Beuren, F. T., Jr.: Lethal Factors in Acute Ileus, Ann. Surg. **75**: 423, 1922.

161. von Khantz, A.: Zur Frage der Bakteriämie bei Ileus und postoperativer Darmlähmung, Arch. f. klin. Chir. **88**:412, 1908-1909.

The great objection to the theory of shock is the meager experimental proof. There cannot be any question about the fact that the picture of high obstruction, whereas it may simulate shock in some respects, is widely different in others. Shock may be an element in some cases, but it cannot possibly explain the whole phenomenon.

Another group of workers claims that death is due to disturbance in the acid-base mechanism and dehydration plus starvation. This has been fully discussed elsewhere. In view of what has been brought out heretofore, it seems evident that they are only dealing with part of the picture. They confine all their work to simple obstruction and do not attempt to explain closed loops or strangulation. Their explanation does not seem to be entirely adequate even for simple obstruction, because toxic symptoms do occur here.

Draper Maury [118] suggested that death may be due to the loss of some internal secretion which is elaborated by the duodenum and small intestine and is essential to life. This is definitely refuted by the fact that dogs will live indefinitely with the entire duodenum removed and have been kept alive three months after the removal of the pylorus, duodenum and upper part of the jejunum.

Ellis [36] said the fact that an identical poison is recovered from the gastro-intestinal tract after toxic injection suggests some physiologic dysfunction.

It seems appropriate, under this heading, to discuss the work of Werelius.[89] He studied drained duodenal loops and noticed that in twenty-four hours the secretion of bile stopped, and the bile was replaced by a clear mucoid or reddish fluid. This change in the character of the biliary secretion predicted serious symptoms and death. He used this as the basis of his theory, in which he claimed that the liver depended for its normal function on the nervous reflexes derived from normal peristalsis. Therefore, if the intestine became aperistaltic for one reason or another, the liver ceased to function, and death resulted from this insufficiency. He applied this to intestinal obstruction, claiming that the intestine below an obstruction became aperistaltic and thus reflected on liver function. In this way he attempted to explain why high obstruction was more fatal then low, i.e., because it resulted in more aperistaltic gut. He claimed that the high amount of urea was not an argument against liver insufficiency, because urea could be formed in other organs as well. This is an original idea, but lacking in experimental proof. It is further weakened by the symptomatology he described in his animals: (1) subnormal temperature, (2) albuminuria, (3) leukocytosis 20,000, (4) low blood sugar, (5) increased urea and (6) low carbon dioxide.

SUMMARY

Certain facts stand out and should be emphasized.

1. In high obstruction two different processes are involved: (*a*) a profound disturbance in the acid-base mechanism resulting in alkalosis and dehydration and (*b*) a definite toxemia. In simple obstruction, the first process is the more prominent and often fills the whole picture. However, toxemia may enter also to a varying extent. On the other hand, in closed loops and strangulation, the toxemia is on the ascendency and often crowds everything else out.

2. There is a toxin in the lumen of the obstructed gut and it looks very much as if it reached the blood stream and was responsible for the toxemia. The origin of this is not clear. Those who say that it is formed by bacteria must prove:

(*a*) Why high is more fatal than low obstruction.

(*b*) Why the toxin appears so rapidly after obstruction.

(*c*) Why the toxin appears in the gut immediately after toxic injection.

(*d*) Why the toxin appears in such conditions as clotting of the portal vein, acute pancreatitis, and bilateral suprarenalectomy, when there is no obstruction.

Those who claim that it is not formed by bacteria must prove its formation in their absence.

3. There seems to be some mysterious connection between the toxemia of high obstruction, acute pancreatitis, bilateral suprarenalectomy and anaphylaxis.

I shall not attempt to draw conclusions myself. I should, however, like to emphasize the fact that more work should be done on strangulation. In this condition, toxemia is developed to its highest degree. The alkalosis and dehydration can be controlled. However, one rarely sees cases of simple obstruction in the clinics without the complication of toxemia; therefore, there remains the necessity of finding a means of combating this dread condition.

What is the cause of death in high obstruction?

URETERAL ACTIVITY IN SOME PATHOLOGIC CONDITIONS

STUDIED BY THE GRAPHIC MANOMETRIC METHOD*

HARRY ROBERT TRATTNER, M.D.
CLEVELAND

In 1924, I published some observations on peristalsis of the intact human ureter obtained by means of a graphic method. Since that time additional physiologic data have been gathered and records taken in a number of pathologic cases.

The object of this work is to throw greatly needed light on the hitherto meager knowledge of the behavior of the human ureter, and to give to the urologist a method that admits of easy application in the clinic, so that it is possible to recognize disturbances of ureteral function.

In a review of the literature it was found that studies devoted to the physiology and physiologic pathology of the human renal pelvis and ureter are comparatively few. More numerous, however, are the investigations which have been conducted on animal ureters, intact and excised.

METHODS OF STUDY

The methods of study of ureteral activity may be classified as follows: (1) ocular observations—direct and indirect; (2) electro-ureterographic, and (3) graphic.

Ocular.—Direct ocular observations are made by exposing a section or the entire extent of the ureter, leaving it in situ, or excising and placing the organ in a bath of oxygenated Ringer's or Locke's solution. Investigations made simply by watching the ureteral waves are obviously inexact, particularly on the intact organ, because of the confusion of ureteral movements with those of the neighboring organs as well as the inability of the eye to follow many of the waves which are either too small or too rapid to be seen. For example, while one follows the wave from the renal pelvis, where it is usually initiated, to the bladder, one or more contractions may have followed the preceding one so closely that when the eyes are again directed to the renal pelvis, these con-

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* From the Department of Urology, Cleveland City Hospital, and the Department of Pharmacology, Western Reserve University.

* The animal investigative part of the work is being assisted by a grant from the Therapeutic Research Committee of the Council on Pharmacy and Chemistry of the American Medical Association.

* Read before the Section on Urology at the Seventy-Ninth Annual Session of the American Medical Association, Minneapolis, May 15, 1928.

tractions have passed unnoticed. If only one point on the ureter is observed, it is difficult to differentiate between local contractions and those that pass the entire length of the ureter.

Indirect ocular observations have been made by watching the activity of the lowermost section of the ureter through the cystoscope. Data obtained in this manner are not wholly reliable because there may be inactivity of the upper and middle portion, while the lower section of the same ureter may be functionally competent.

Studies of ureteral activity have also been conducted with the aid of the fluoroscope either during or after the injections of opaque solution. This method is open to the following objections:

1. The view is not sufficiently clear because of diffusion by intervening tissue and organs.

2. Only short observations are possible because of the danger of overexposure to the roentgen ray.

3. The intra-ureteral injection of any fluid toward the renal pelvis gives rise to abnormal activity of various degrees depending on the pressure of injection, the position of the catheter in the ureter, the amount, kind and strength of solution employed.

Thus the emptying time of the renal pelvis could be hastened or delayed through a physiologic disturbance of the nature of hyperactivity, spasticity or temporary abolition of peristalsis.

Electro-Ureterographic.—In 1914, Orbeli and Brucke obtained electro-ureterograms in the rabbit by placing two electrodes a short distance apart on the outer wall of the ureter and attaching them to a galvanometer. They found that the smooth muscle of the ureter in situ, delivers rhythmic current variations of the triphasic ground type. I have attempted to obtain an electro-ureterogram from the intact human ureter by placing one electrode in the ureteral lumen and the other on the skin in the region of the renal pelvis, the electrodes being connected to the electrocardiograph. The result was that cardiac contractions were found superimposed on other current variations which probably represent ureteral current phenomena. Thus far this method has not been found applicable to the intact unexposed ureter.

Graphic.—Records of ureteral peristalsis have been obtained in animals by graphic methods as follows:

1. A rubber capsule is bound to one end of a catheter which is inserted into the ureter and the capsule ballooned out, the free end of the catheter being connected with an ordinary recording tambour. Fagge first recorded contractions from the intact animal ureter by this method. The objection to this procedure is that there is partial or complete obstruction to the flow of urine with the resultant effect of an increasing intra-ureteral pressure.

2. A cannula is inserted into the ureter, the cannula being attached to a water manometer and this to a piston recorder. Lucas and Satani employed this method, but no description is given of the manner in which the urine was prevented from accumulating.

3. Muscle levers are attached to the ureteral wall. This method records the activity of the longitudinal muscular coat. Obviously it cannot be used on the intact unexposed ureter.

4. The New Graphic Method: The chief objection to the work on the intact organ has been the lack of an adequate method. This difficulty has, I think, been overcome in the apparatus herein described, because (*a*) ureteral activity is recorded while permitting a practically unobstructed urinary escape; (*b*) the method is adaptable to the intact unexposed human ureter as well as to the exposed or excised animal ureter, and (*c*) the method is of minimum inconvenience to both patient and operator.

The manometer, although the same as the earlier model in principle, has been improved so that it is more sensitive and easier of manipulation. In order to establish the degree of peripheral resistance at which contractions are most satisfactorily maintained and to simulate intravesical pressures, a finely threaded screw adjustment is now employed, thus permitting a regulation of the outflow to any desirable extent (fig. 1). By means of this instrument, graphic records have been taken from man, and from the dog and rabbit. Consecutive tracings have been taken for as long as ten hours from the intact and excised ureter of the dog. In the human studies, a comparison of the activity of the ureter of one side is usually made with that of the other by using one manometer alternately. The upper, middle and lower portion of the ureter may be examined separately by placing the end of the catheter at the desired level. Simultaneous records of the activity of both ureters have been made by employing two manometers. In a case of bilateral complete ureteral duplication, a simultaneous tracing was taken from all four ureters with four manometers.

By this method the activity of the circular muscle of the ureter is recorded, but since the longitudinal and circular muscles (the latter being composed of more muscle fibers, and therefore the stronger of the two coats) usually contract simultaneously, the record obtained is a fair representation of ureteral activity.

In my first paper it was pointed out that the ureter seems to possess two chief types of waves, namely, the small more rapid pendulum movements that are not concerned with the propulsion of urine, and the slower more powerful peristaltic contractions that are usually accompanied by an outflow of urine. The rate and amplitude of these types

of waves vary, and they may be further subdivided into waves of various configurations. Ureteral tonus variations, tonic and spastic contractions may also be found. There may be a succession of various types of waves, they may be superimposed on each other, or the activity may be limited to one type only. Pressure on the ureter, changing the position of the patient (from recumbent to standing), moving the catheter, etc., usually alters rhythmical activity. Spontaneous alterations in rhythm may also occur.

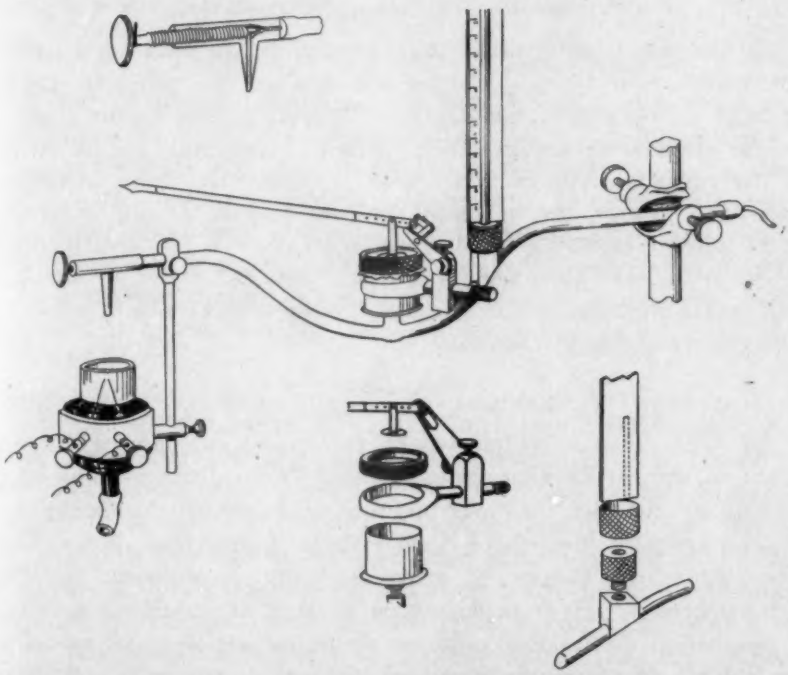

Fig. 1.—Diagrammatic drawing of the improved water manometer for the recording of ureteral peristalsis. The drop recorder is attached to the manometer (Biskind, M. S., and Dan, M.: An Automatic Drop Recorder, Proc. Soc. Exper. Biol. & Med. **26**:52, 1928). Tambour cup, scale and lever mounting are removable. A longitudinal section of the outlet screw adjustment is shown.

Ureteral contractions may also be classified as (1) complete, i. e., those that pass the entire length of the ureter, (2) incomplete, i. e., those that arise in the renal pelvis but disappear before reaching the bladder, and (3) local, i. e., those which are confined to a small segment of the ureter. The manometer records the complete contractions and many of the incomplete ones, and when the latter immediately follow the former, the character of the waves is frequently bigeminal or trigeminal.

PATHOLOGIC PHYSIOLOGY

One of the many but not the least important factors on which normal renal physiologic activity depends is a functionally competent ureter, because urine is conducted from the renal pelvis to the bladder chiefly through peristalsis. Other factors aiding in the conduction of urine, such as renal filtration pressure, gravity, the action of the diaphragm, movements of the colon and its contents, play a secondary rôle. Of the latter factors, the filtration pressure is the most important.

TYPES OF URETERAL OBSTRUCTION

In the past most attention has been devoted to mechanical ureteral obstruction. In many instances the problem of effective ureteral drainage is not one of this nature. Ureteral obstruction may also be of the dynamic variety in which there is hypertonus, spasm, etc., or of the adynamic type in which there is hypotonus, atony, atrophy or paralysis. Just as atonia, spasm and paralysis occur in the intestine in the absence of mechanical factors, so the same is also true in regard to the ureter. If the ureter is spastic, hypotonic, atonic or paralyzed or if it is prevented from contracting by being bound down by adhesions, then perfect drainage is impossible.

DILATATION IN THE ABSENCE OF MECHANICAL OBSTRUCTION

In 1919, Braasch commented on atonic and inflammatory ureteral dilatation without mechanical obstruction. In another paper, he stated, "When we consider the large number of cases of chronic bilateral pyelonephritis in which there is evidence of ureterectasis, it is striking how seldom the degree of actual stricture is sufficient to cause hydronephrosis." Hydronephrosis and ureteral dilatation in the absence of mechanical obstruction could, no doubt, be due to stasis caused by the inability of the ureter to propel its contents efficiently. A factor that contributes to the formation of a dilated ureter and renal pelvis is that the atonic ureter is now an open tube, subjected to renal filtration pressure from above and particularly when there is incompetency of the ureteral orifice and intramural ureter also to the peripheral resistance of the various bladder pressures below. A condition on which the formation of ureteral dilatation depends, appears to be the absence of any appreciable degree of peri-ureteritis or para-ureteritis because the latter may encase the ureter to such an extent as to prevent wholly or partially the development of distention.

Stewart and Barber offered for consideration the following: "Adynamic ureteral obstruction may give rise to distended kidney." They stripped the ureter of its nervovascular connections throughout its course, and produced a purulent cystitis. They concluded that

"paralysis of the ureter is accompanied by urinary stasis and kidney distention in 66 per cent of cases, and that the pathological changes in hydronephrosis of functional origin correspond to the age of the adynamic ureter."

Incompetency of the ureteral musculature would account for (1) the unilateral dilatation sometimes seen when the obstruction is distal to the ureter (e. g., urethral stricture and obstructions of the neck of the bladder), for if the dilatation were due to back pressure alone, both ureters should be involved, and (2) the resistance to treatment in many cases of ureteropyelitis.

A TEST OF URETERAL COMPETENCY

A test for ureteral competency is usually carried out when there does not appear to be any spontaneous peristaltic activity, because it is then not known whether the ureter is merely quiescent, or whether it is incapable of contracting. The test is based on the fact that when fluid (water, saline, etc.) is injected into a ureter capable of contracting, there is immediately elicited energetic attempts at expulsion. The motor response varies according to the degree of ureteral involvement, and is designated as strong, moderate, feeble or absent (fig. 2).

URETERITIS

The clinical conceptions of O. T. Thomas in regard to ureteritis are of importance in understanding the behavior of the female ureter. The blood supply to the lower half of this organ is obtained through branches of the ovarian, uterine and superior vesical arteries. He has long held (1906) that the increased vascularity occurring at the menstrual period, during pregnancy and in those pathologic pelvic conditions that give rise to increased blood flow, often accounts for the pain and the lighting up of a latent urinary tract infection. The pain ordinarily designated as dysmenorrhea, he believed to be really ureteral in character. This occurs most often in those persons whose ureters (one or both) are found to be thickened or tender (ureteritis) on vaginal examination. These patients complain of backache, pelvic pain or pain referred along the entire course of the ureter and frequently associated with disturbances of urination. In many of these cases the pyelo-ureterogram appears normal, no obstruction is detectable with a catheter, and urinary tract infection may or may not be present.

That congestion of the ureter occurs frequently during menstruation and pregnancy has been observed at autopsy, little or no congestion being found in the other organs. Thomas said that "the recurring congestion with each menstrual period is a most important factor in prolonging the catarrhal process." Whether the increased blood flow to the lower ureter causes a mechanical impediment to urinary drainage

through congestion or edema, or whether increased vascularity in itself is sufficient to modify ureteral peristalsis to such a degree as to give rise to a dynamic type of ureteral obstruction, by reason of the ureter's hypertonic state, is not definitely known. No doubt, both of these factors play their respective rôles. That ureteral contractions may give rise to pain seems certain, for pain is often experienced each time the lever of the manometer traces a wave, or if there is no actual pain, the patient can often indicate each contraction as it is traced.

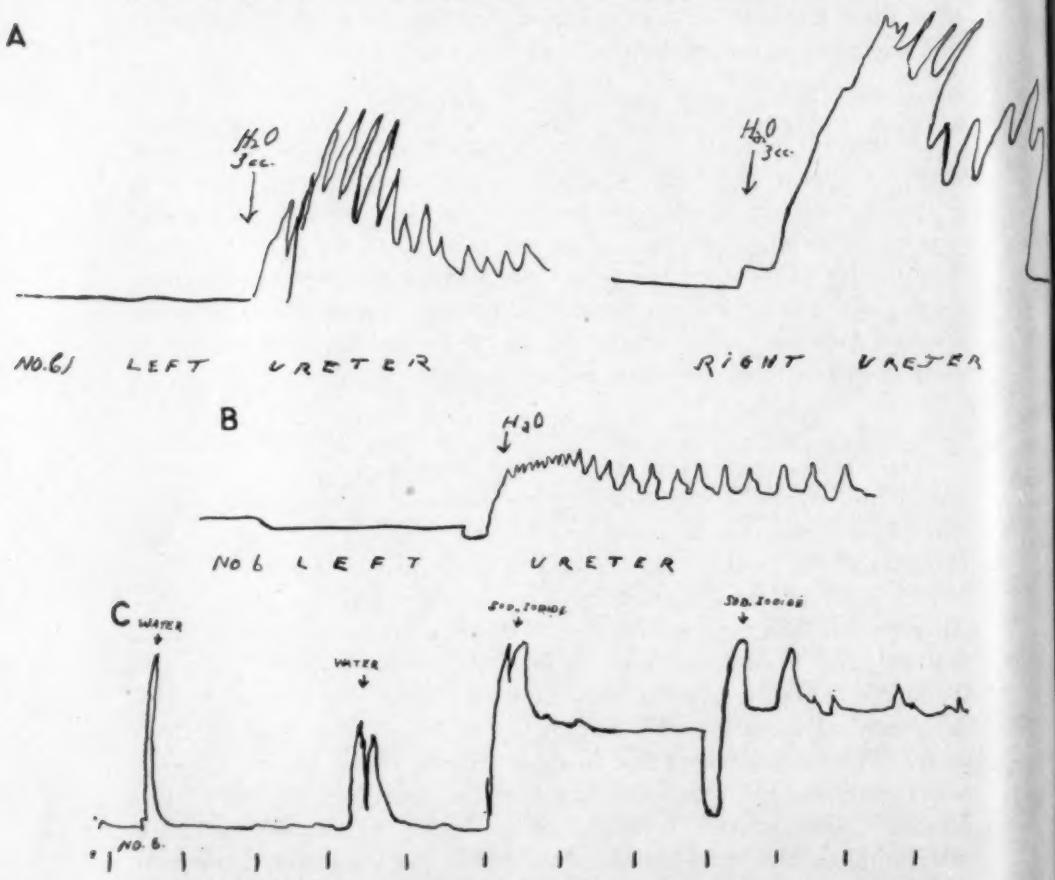

Fig. 2.—The motor response of the ureter to the intra-ureteral injection of solution. This is a test of ureteral competency in the absence of spontaneous peristaltic activity. *A* represents a strong motor response to the intra-ureteral injection of water; *B* a moderate motor response to same, and *C*, a feeble motor response since four intra-ureteral injections were required before peristaltic contractions were obtained and these were of very small amplitude.

In 1897, Protopopow demonstrated on dogs that increased blood flow to the ureter (pressure on the vena cava above the renals) accelerated its action, while decreased blood flow (pressure on aorta above

the renals) diminished the frequency of ureteral movements. These experiments are to be repeated in the light of modern methods of investigation.

Ureteritis can be classified as (1) simple, and (2) that which is secondary to tuberculosis, calculous disease, etc., or associated with the same. In general, it can be said that the cases fall into one of three divisions according to the degree of ureteral activity present, as follows:

First Degree Ureteritis.—Hyperactivity, hypertonus.

Cases belonging to this division are those in which an early toxic or inflammatory process, that is evidently irritative, is present. The patient usually complains of acute, colicky pain. On vaginal examination, there is tenderness along the course of one or both ureters. The manometric tracing shows a marked increase in amplitude and rate of peristaltic waves, or there may be prolonged tonic contractions (spasm). The motor response to the intra-ureteral injection of fluid is strong, the patient complaining of severe pain when as small a quantity as from 2 to 5 cc. is gently injected. Ureters in this class may recover their normal activity, or there may be a progression into the second degree. The following cases illustrate this division:

Case 1.—B. B., a woman, aged 18, complained of nausea and acute pain in the lower part of the abdomen. Three years before she had had an attack of high fever with pain in the back (ureteropyelitis?) appearing evidently at the time of the beginning of her menstrual life. There was exquisite tenderness in the region of both ureters on vaginal examination, and on the right and left sides of the abdomen. There was no fever. Cystoscopic examination showed normal observations. Manometric tracings showed a marked hyperactivity of both ureters (fig. 3 *B*).

Case 2.—M. F., a woman, aged 22, complained of pain in the right side of the abdomen and a continuous flowing since the last menstrual period. One week before she had had chills, fever and vomiting; at the time of the report she was afebrile. Five years before she had had an acute right suppurative focal nephritis, at which time a right nephrectomy was done. There was tenderness along the course of the left ureter both on abdominal and vaginal examination. Cystoscopic examination revealed a mild colon bacillus infection.

Manometric tracing showed the presence of waves of great amplitude, and there occurred as many as fifteen contractions in less than one minute (fig. 4).

Case 3.—M. K., a woman, aged 30, complained of backache and abdominal pain referred to the labia. One year before she had had an appendectomy, salpingectomy and ventral suspension of the uterus without relief. On vaginal examination, there was tenderness over the course of the ureters. On cystoscopic examination, red blood cells were found in the specimen of urine from the left side.

Manometric tracing showed prolonged tonic contractions with short periods of relaxation.

Second Degree Ureteritis.—Hypotonus, atonia.

The cases belonging to this division are those in which ureteral activity is being, or has been, interrupted by toxic factors, inflammatory

infiltration or thinning of the muscular coats through dilatation. The pain is usually more constant and dull rather than acute, but there may be acute exacerbations of pain. On vaginal examination, one or both ureters are found to be palpable and tender to pressure. The manometric tracing shows either a marked decrease in amplitude or total abolition of the peristaltic contractions. There is either a feeble

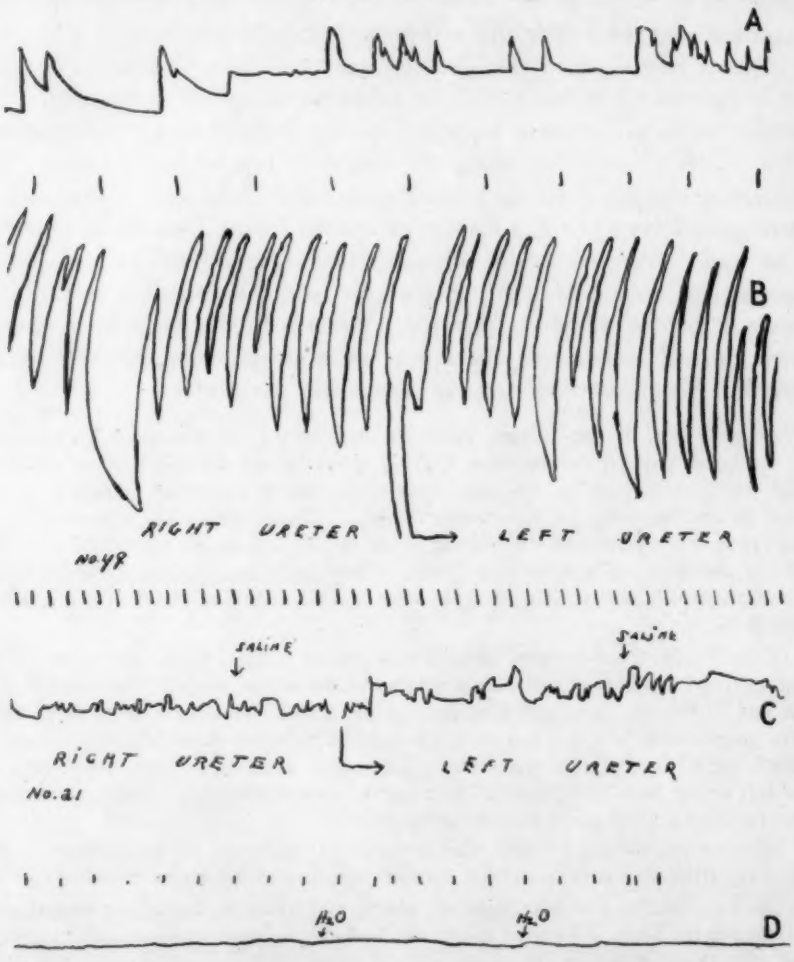

Fig. 3.—Typical tracings of the progressive degrees of ureteritis. *A* represents one type of a normal tracing; *B*, first degree ureteritis. There is an increase in the amplitude and rate of contractions (case 1). *C* is a tracing of second degree of ureteritis. There is a decrease in amplitude of contractions and there is little if any motor response to the intra-ureteral injection of saline. The ureters are hypotonic (case 4). *D* is a tracing of third degree ureteritis. There are no spontaneous contractions, and no motor response could be elicited by intra-ureteral injections of water. This demonstrates atonia or paralysis (case 26).

or no motor response to the intra-ureteral injection of fluid, which may return slowly or not at all through the catheter (even though the catheter fits the ureteral orifice snugly enough to prevent backflow of fluid along side it into the bladder). Ureters in this class may recover their activity, or there may be a progression of the process into that of permanent paralysis. The following cases are illustrative of this division:

CASE 4.—C. J., a woman, aged 28, complained of abdominal pain, dysuria and frequency of urination for the past four weeks. For the past two days, she had had chills and fever (104 F.). The patient had had a similar attack fourteen years before.

On examination, tenderness was found in the lower part of the abdomen. Both ureters were palpable and tender vaginally. Cystopic examination revealed a bilateral mixed infection (cocci and gram-negative bacilli). Bilateral pyelo-ureterograms appeared normal.

Fig. 4 (case 2).—First degree ureteritis. There is an increase in amplitude and an intermittent increase in the rate of contractions.

Manometric tracing showed hypotonus of both ureters (fig. 3 *C*).

CASE 5.—B. S., a woman, aged 20, had a condition clinically diagnosed pyelitis of pregnancy. Several hours after delivery, she had had a chill and complained of pain in the left lumbar region. For the past week there had been a dull pain radiating to the groin on this side.

On examination a week later, costovertebral tenderness was found on the left side; both ureters were thickened on vaginal examination. Cystoscopic examination showed right colon bacillus infection. Right pyelo-ureterogram showed a slight ureteral dilatation. Manometric tracing showed powerful peristaltic waves on the right side (ureteritis of first degree), atonic relaxed left ureter, there being no response to the injection of water; bimanual pressure of the left kidney was transmitted through the ureter. A tracing taken six days later showed that the right ureter was now also atonic. On this side, there had been a progression from ureteritis of the first degree to that of the second degree (fig. 5).

CASE 6.—A. B., had a condition clinically diagnosed subacute ureteropyelitis. She complained of pain in the right side of the abdomen radiating to

the back and thigh. There had also been nausea and vomiting. She was in the hospital three weeks before with the same complaint. Cesarean section had been done four months before.

On examination, tenderness was found in both lower abdominal quadrants and over the renal regions posteriorly; both ureters were palpable and tender vaginally. Cystoscopic examination showed a thick exudate coming from the right ureteral orifice. Infection was found only on the right side. Bilateral pyelo-ureterograms showed slight or moderate ureteral dilatation. Catheters were left in the ureters for twelve hours.

Manometric tracing showed atonicity of both ureters, there being no response to injections of water. A tracing repeated one week later, showed recovery of

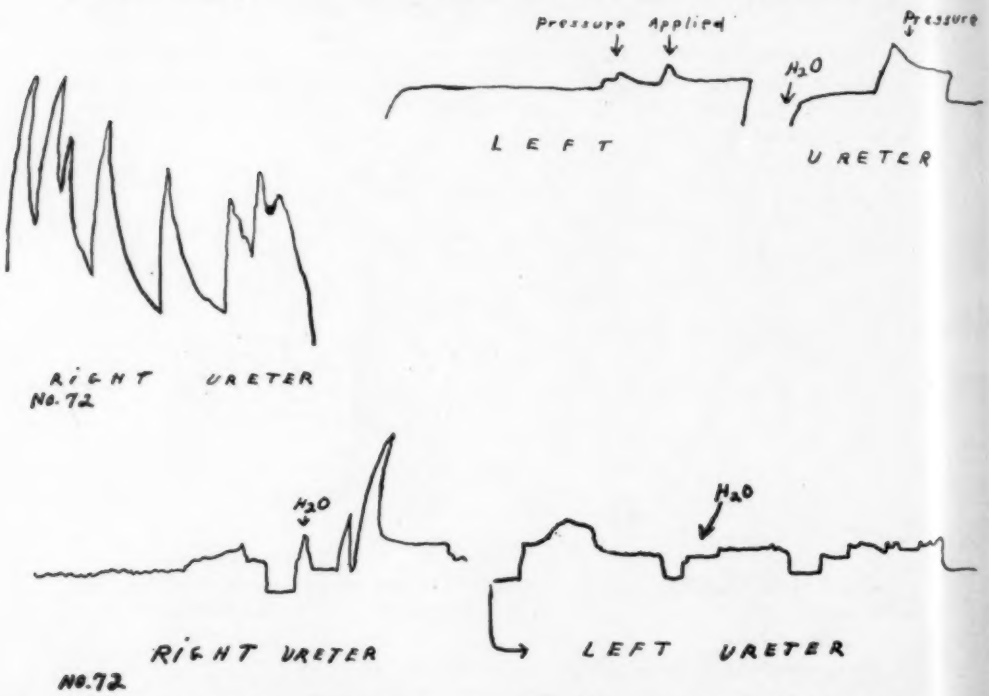

Fig. 5 (case 5).—The top tracing shows the left ureter to be atonic or paralyzed and the right ureter to possess a slight increase in activity. The lower tracing (taken six days later) shows hypotonicity of both ureters. There has been a progression from ureteritis of the first degree to that of the second degree on the right side.

activity of both ureters. At this time, the patient feels well and is free from symptoms (fig. 6).

CASE 7.—H. S., a woman, aged 31, had a condition clinically diagnosed ureteropyelitis of pregnancy (puerperal). She complained of backache and abdominal pain; she had had spontaneous normal delivery. A catheterized specimen of urine contained many white blood cells.

Cystoscopic examination showed a bilateral mixed infection (cocci and bacilli) with many white blood cells from each side. Pyelo-ureterograms showed bilateral

dilatation of mid and upper ureters, also bilateral renal pelvic dilatation. The lower ureters, however, appeared normal in size.

Manometric tracing taken from the upper, mid and lower ureters on the right and left sides showed the absence of peristaltic activity in the mid and upper portions, while the lower undilated sections still had some contractile power, though they were hypotonic (figs. 7 and 8). The left pyelo-ureterogram was similar to that of the right side in appearance.

It is known that every portion of the excised ureter is capable of independent contractions. This case demonstrates that this may also be true of the intact unexposed ureter.

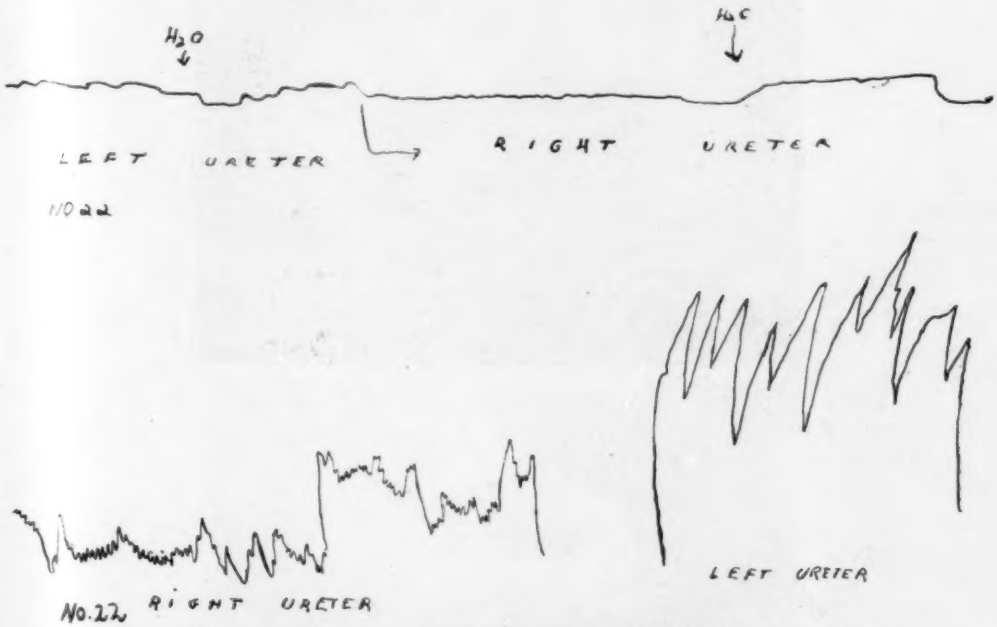

Fig. 6 (case 6).—The top tracing shows atonia of both ureters. The lower tracing (taken one week later) shows a recovery of activity on both sides.

Case 8.—C. K., a woman, aged 35, complained of abdominal pain on the right side radiating to the back and groin. The pain was more severe when lying down than when being up and around, and also immediately prior to menstruation. There was dysuria, frequency and hematuria. A right pyelo-ureterogram showed a dilatation of the ureter and renal pelvis. Nine months later, a repeat pyelo-ureterogram showed the ureter restored to a normal caliber and the pelvis not so markedly dilated. Even though this is true, the manometric tracing taken at this time showed the right ureter to have only pendulum movements, there being no motor response to water. The pressure produced by bimanual compression of the kidney was repeatedly transmitted to the manometer, thus showing that the right ureter was still atonic and relaxed. The left ureter possessed spontaneous peristaltic waves (figs. 9, 10 and 11).

Fig. 7 (case 7).—Right pyelo-ureterogram showing a dilatation of the ureter above the first sacral vertebra. The lower ureteral section is normal in outline. From a case of puerperal ureteropyelitis.

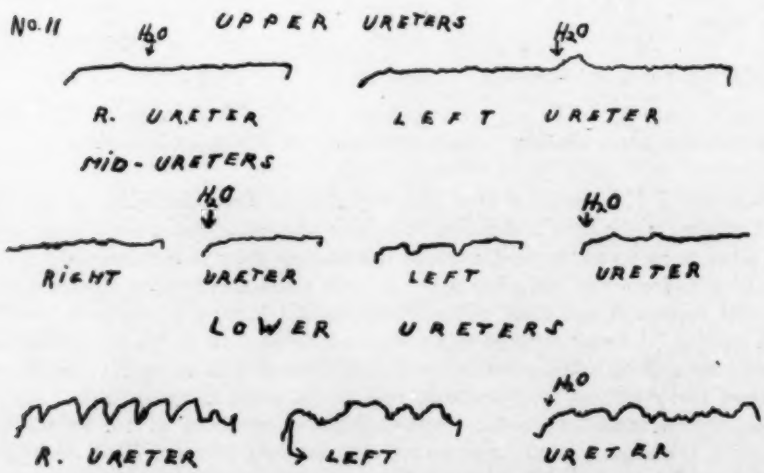

Fig. 8 (case 7).—Tracings from the upper, middle and lower sections of both sides showing activity only in the lower undilated portions of the ureters. There is atonia of the upper and middle sections and hypotonus of the lower sections.

Fig. 9 (case 8).—Right pyelo-ureterogram showing a moderate dilatation of ureter and pelvis.

Fig. 10 (case 8).—Pyelo-ureterogram, taken nine months later, showing a restoration of the ureter to a normal caliber.

CASE 9.—L. B., a woman, aged 20, emaciated, had a condition clinically diagnosed: ureteropyelitis and peri-ureteritis. She complained of fever, pain in the right part of the back, loss of weight and frequency of urination of five weeks' duration.

On examination, tenderness was found in the right side of the lower part of the abdomen and right renal region. Cystoscopic examination revealed a bilateral infection (gram-positive cocci). Many white blood cells were found in specimens from both sides. The catheter passed on the right side, met an obstruction 17 cm. up on one occasion (verified by ureterogram), and on another occasion, no obstruction was encountered (also verified by pyelo-ureterogram).

Manometric tracing showed bilateral loss of ureteral activity. Two months later, after the patient had been relieved of her symptoms and pelvic lavage with mild silver protein given, the tracing showed the right ureter to have recovered a slight amount of activity, and the left ureter to have completely recovered its contractile power.

CASE 10.—A. P., a woman, aged 24, single, complained of chills, fever and pains in the back. For the past four or five years, she had had attacks of abdominal and lumbar pain at the menstrual period. As a child, she had been a bed wetter.

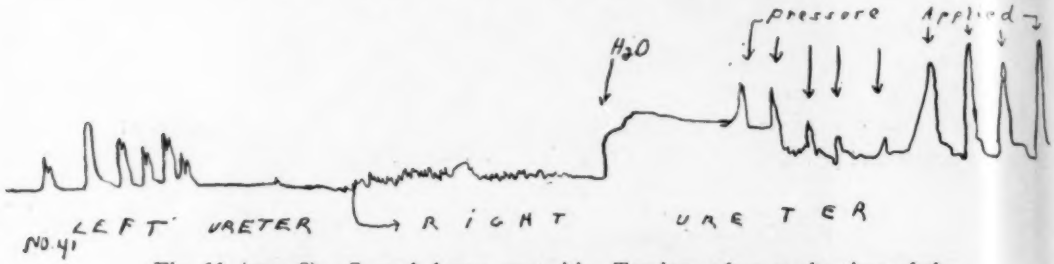

Fig. 11 (case 8).—Second degree ureteritis. Tracing, taken at the time of the last pyelo-ureterogram (which appears normal) shows the right ureter to be atonic and relaxed throughout, since pressure applied to the kidney is transmitted to the manometer.

The temperature was 104 F.; the urine contained many white blood cells. On examination, tenderness was noted over the right and left kidneys and along the course of both ureters, particularly the left. Both ureters were palpable and tender on vaginal examination. A left pyelo-ureterogram showed an absence of fluid in the lower section of the ureter; otherwise it was normal.

A clinical diagnosis was made of acute ureteropyelitis superimposed on a chronic ureteritis. Manometric tracings taken on three different occasions showed hypotonicity of both ureters and practically no response to intra-ureteral injections of water.

CASE 11.—A. W., a woman, aged 35, complained of dysuria and dull abdominal pain radiating into the groin and pain in the back, particularly on the left side. The pain was more acute during menstruation. She had had this trouble for the past ten years. A pelvic operation was done four years before without relief. On examination, tenderness was found along the entire course of the left ureter and in the left renal region. The right ureter was thickened and tender on vaginal examination. The left ureter was not palpable, but there was tenderness to light pressure in that region. Urinalysis was negative. Nothing abnormal was found on cystoscopic examination. A bilateral pyelo-ureterogram appeared normal.

Manometric tracing showed a tendency to increased peristaltic activity on the left side, while hypotonus was found on the right side, there being no response to the intra-ureteral injection of water.

A diagnosis of ureteritis of second degree on the right side and first degree ureteritis on the left (?) was made.

NOTE: It is interesting to note that the patient complained of pain on the left side even though examination shows more involvement of the right ureter.

CASE 12.—E. H., a woman, aged 19, with puerperal pyelitis, seventeen days after normal delivery, full term pregnancy, had a temperature rising to 39 C. (102.2 F.), accompanied by marked tenderness over the right renal region, also some tenderness over the left renal area. The urine contained many white blood cells. The ureters were palpable on vaginal examination; the left felt thicker than the right.

Cystoscopic examination showed +++ white blood cells in urine from the left side and ++ white blood cells in urine from the right side. There was staphylococcus infection. Pyelograms were not made. Manometric tracing showed a complete abolition of activity of the left ureter and a diminution of activity of the right ureter. It is of interest to note that the patient complained of pain on the side that examination shows to be the least involved.

CASE 13.—V. C., a girl, aged 16, complained of pain in the back and lower part of the abdomen, dizziness and nausea. The patient stated that this trouble began one year before, immediately after her first intercourse. Menstruation occurred twice a month, the flow lasting for eight days. On examination, tenderness was found in both lumbar regions. On vaginal examination, there was tenderness along the course of both ureters, but they were not palpable.

Cystoscopic observations showed nothing abnormal. Manometric tracing showed inactivity of both ureters. Tracing repeated two weeks later, showed recovery of activity of both ureters. At this time the patient feels well and is symptomless.

Often it is rather difficult to make a dogmatic classification of some of the cases, since a late second degree ureteritis may belong to that of the third degree. It is unusual for recovery of activity to occur in the latter division, but it is possible in some instances, particularly in some cases of ureteropyelitis of pregnancy in which extreme ureteral dilatation is present, and after a year or longer the ureter may recover its normal caliber and activity.

Third Degree Ureteritis.—Paralysis.

Cases belonging to this division are those in which peristaltic ureteral activity has been permanently abolished because of extensive inflammatory infiltration (fibrosis) or because of thinning of the muscular coats by marked dilatation (atrophy). On vaginal examination, the ureter is found to be thickened in most instances, and there may or may not be tenderness to palpation. The manometric tracing shows complete absence of peristaltic activity, there being no response to intra-ureteral injections of fluid. Cases 14 and 15 are illustrative of cases in which tuberculosis of the kidney with ureteral involvement occurs.

CASE 14.—C. U., had tuberculosis of the right kidney with extensive ureteral involvement. The right ureter was palpable vaginally. Manometric tracing did not show any activity of the right ureter, there being no motor response to intra-ureteral injections of saline. The left ureter possessed some peristaltic activity.

Right nephro-ureterectomy was performed. The ureteral specimen showed extensive infiltration. The right pyelo-ureterogram did not show the degree of involvement actually present (figs. 12, 13 and 14).

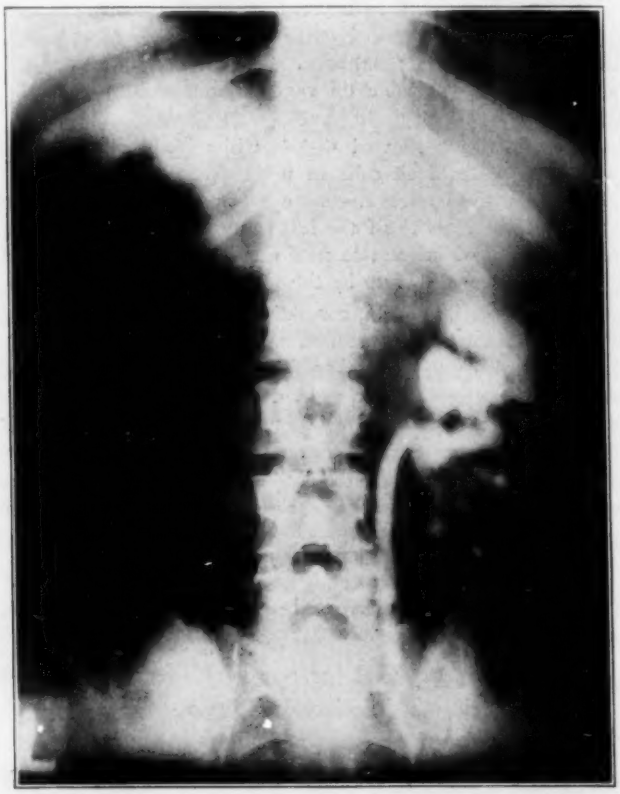

Fig. 12 (case 14).—Tuberculosis of the kidney with ureteral involvement. Right pyelo-ureterogram. The pelvic and renal portions are typical of tuberculosis, while the outline of the ureter did not reveal the extensiveness of ureteral involvement found at operation.

CASE 15.—W. D., had left tuberculous pyonephrosis with extensive ureteral involvement. Manometric tracing did not show any spontaneous activity of the left ureter, and after two intra-ureteral injections of saline, there were pendulum but no peristaltic waves. The right ureter showed little spontaneous activity, but there was a peristaltic response to the intra-ureteral injection of saline. Left nephrectomy was performed. The ureter, as far as it could be seen at operation, was extensively infiltrated but could not be removed because of marked adhesions.

Case 16 is illustrative of a case of tuberculosis of kidney without ureteral involvement.

CASE 16.—E. H., had tuberculosis of the left kidney without ureteral involvement. Manometric tracing showed both ureters to possess peristaltic activity. Left nephro-ureterectomy was performed. The ureter looked and felt normal (figs. 15 and 16).

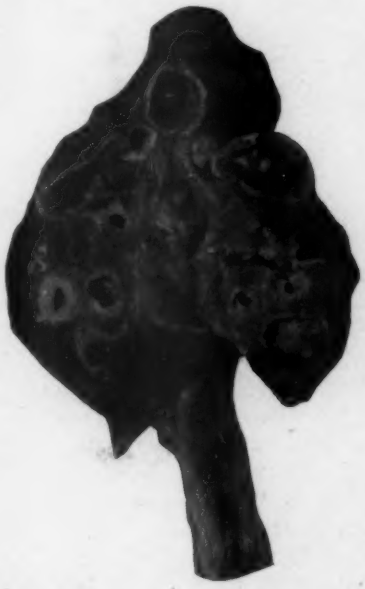

Fig. 13 (case 14).—Operative specimen showing extensive ureteral infiltration.

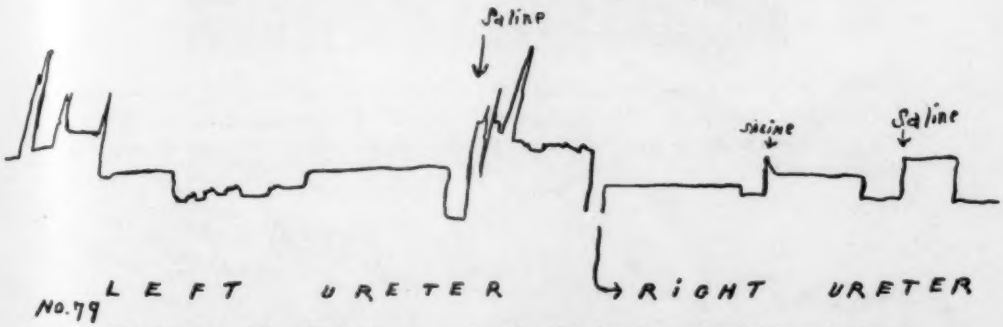

Fig. 14 (case 14).—Third degree ureteritis. Tracing from the right ureter shows a complete absence of peristalsis. The left ureter possesses spontaneous activity.

Cases 17, 18, 19, 20 and 21 are illustrative of cases of lithiasis in which manometric tracings are made.

CASE 17.—M. F., had multiple stones in the left kidney and a left lumbar fistula. Left nephrectomy was performed. Manometric record showed the right ureter to possess normal peristaltic activity. The left ureter did not show any

activity spontaneously, nor any response to intra-ureteral injections of water or saline (figs. 17 and 18).

Case 18.—F. F., had left renal lithiasis. Manometric tracings taken on two different occasions did not show any activity of the left ureter, spontaneously or

Fig. 15 (case 16).—Tuberculosis of the kidney without ureteral involvement. Left pyelo-ureterogram. The pyelogram is typical of tuberculosis of the kidney; the ureterogram shows some dilatation and a suspicion of the presence of ureteral involvement.

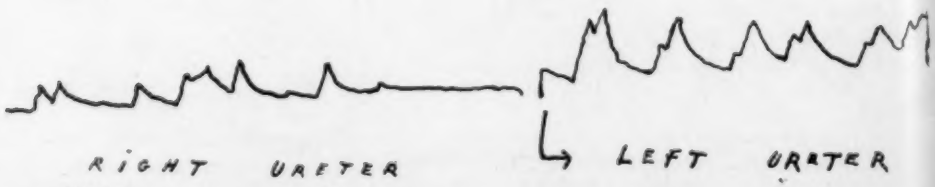

Fig. 16 (case 16).—Tracing showing both ureters to possess peristaltic activity. The operative specimen did not show any evidence of ureteral involvement.

after the intra-ureteral injection of water. The right ureter had pendulum movements, and a low grade of peristaltic activity, there being only a feeble response to the injection of water on this side.

Fig. 17 (case 17).—Renal lithiasis with infection. Ureteral infiltration. The left ureterogram shows obstruction of the upper ureter and multiple stones in the left renal area.

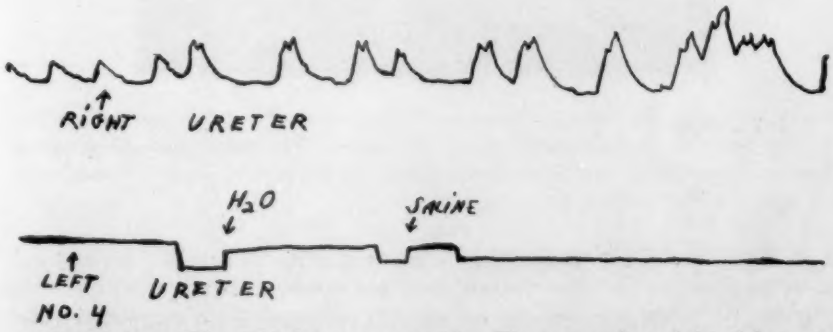

Fig. 18 (case 17).—Third degree ureteritis. The top tracing of the right ureter shows normal activity; the lower tracing is that from the left ureter and shows complete cessation of function.

Left nephro-ureterectomy was performed. The left ureter was found to be markedly infiltrated. The patient died. The right ureter was removed at autopsy and was found to be the seat of early infiltration. The left pyelo-ureterogram did not reveal the extensive ureteral involvement found (figs. 19, 20 and 21).

CASE 19.—H. E., had bilateral ureteral stones and a right perirenal abscess. Manometric tracings showed bilateral atonia. Two days later (after a stone on the left side had passed) the pressure tracing showed a hypotonic left ureter and atonia of the right ureter.

Fig. 19 (case 18).—Renal lithiasis with infection. Extensive ureteral infiltration on one side, early infiltration on the other. The right pyelo-ureterogram shows moderate pelvic and ureteral dilatation. In the area of the left kidney there is a large shadow which is that of calculi.

CASE 20.—N. S., had stricture (which has been dilated) of the left lower ureter following ureterolithotomy performed three and one half months previously. At operation, the ureter appeared and felt normal; afterward there was wound infection communicating with the ureter. The left pyelo-ureterogram appeared normal, and the infection had completely cleared up at the time the tracings were taken.

Manometric tracing showed both ureters to possess good peristaltic activity. It is of interest to note that ureteral activity was not permanently arrested, even though there had been a severe infection.

Fig. 20 (case 18).—Operative specimen showing a kidney with a large calculi and a markedly infiltrated ureter.

Fig. 21 (case 18).—Third degree ureteritis, left ureter; second degree ureteritis, right ureter. The tracing shows cessation of function of the left ureter and a low grade of activity of the right ureter.

CASE 21.—F. K., a man, aged 42, complained of severe pain (ureteral colic) on the left side. X-ray and cystoscopic examination showed a stone in the left lower ureter. A week later, the stone had passed spontaneously.

Manometric tracing (taken one week after the passage of the stone) showed the left ureter to have diminished contractile ability, and the right ureter to possess a normal peristalsis.

URETERAL DILATATION

The normal ureter is usually not patent throughout, for while it is in systole in one small segment, it is in diastole in another. It has been

Fig. 22 (case 22).—Operative specimen. Kidney with double ureters. There is pelvic and ureteral dilatation.

found unusual for the pressure by bimanual compression of the kidney, or increased intra-abdominal pressure to be transmitted to the manometer through a hypertonic or normal ureter. If the pressure is transmitted, the ureter is either relaxed throughout momentarily or is atonic without dilatation, or there is dilatation without complete mechanical obstruction. The manometric tracing together with the pyelo-ureterogram furnishes complete data in regard to this. In some of the cases a tentative diagnosis of hydro-ureter was made and confirmed by the pyelo-ureterogram (cases 22 and 23).

CASE 22.—G. N., had right hydronephrosis and hydro-ureter. Manometric tracing showed a complete absence of activity of the right ureter, there being no motor response to the injection of water. Deep renal compression was transmitted to the manometer. A tentative diagnosis of dilated ureter was made and confirmed by pyelo-ureterogram and operation (figs. 22 and 23).

CASE 23.—J. R., a man, aged 43, had right hydronephrosis and hydro-ureter (infected, renal calculi).

Manometric tracing showed that the right ureter had no spontaneous activity and that there was no motor response to the injection of water, while the left ureter had a normal peristaltic activity. Pressure produced by bimanual compression of the right kidney can be repeatedly transmitted to the manometer. The foregoing diagnosis, made tentatively, was confirmed by the pyelo-ureterogram and operation.

CASE 24.—G. M., had puerperal ureteropyelitis. Pyelo-ureterograms showed marked bilateral ureteral dilatation with kinking of the middle of the left ureter. Manometric tracings, taken on two different occasions, showed both ureters to be without peristaltic activity, there being no motor responses to the injection of water. Pressure, produced by bimanual renal compression was transmitted to the manometer on the right side, but because of the presence of a ureteral kink there was no transmission of pressure on the left side.

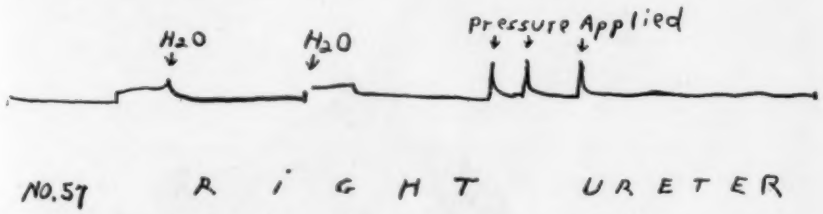

Fig. 23 (case 22).—Tracing showing inability of the ureter to contract. Pressure produced by bimanual compression of the kidney is transmitted to the manometer. Because of this, a tentative diagnosis of dilated or relaxed ureter was made and confirmed. It is not known from which ureter the tracing was taken.

CASE 25.—M. B., had carcinoma of the cervix with extension and compression of the right lower ureter. There was a moderate dilatation of the ureter and pelvis above the obstructed area.

Manometric tracing showed a complete absence of activity of the right ureter, there being no motor response to water injection, while the left ureter has spontaneous peristaltic activity.

Case 26 is illustrative of one in which diffuse fibrosis occurred.

CASE 26.—A. C., a woman, aged 39, had diffuse fibrosis of the ureter and perinephritic abscess. Manometric tracing of the right ureter did not show any peristaltic activity, there being no motor response to injections of water (figs. 24 and 3 *D*).

PERISTALTIC ACTIVITY IN THE PRESENCE OF CORD BLADDER

Three patients were examined, one having syphilitic transverse myelitis, the other two having tabes. No interference with ureteral

activity could be demonstrated. Infection was absent in all. These were evidently early cases, but in those of long standing, particularly when associated with infection, hypotonus or paralysis of the ureteral musculature would, no doubt, be present.

Fig. 24 (case 26).—Autopsy specimen of kidney, ureter and bladder. There is a diffuse fibrosis with shortening of the ureter. There are perforating ulcers in the lower ureter. See figure 3 *D* for manometric tracing from this ureter.

THE MANOMETRIC TRACING AND THE PYELO-URETEROGRAM

Frequently evidence of ureteral involvement is not discernible from the plates, made after injections of opaque solution, even though it is known that such probably exists. This is particularly true of ureteritis

of the first and second degree, while in cases belonging to the third degree, the pyelo-ureterogram does not always reveal the true extent of involvement. Given a normal pyelo-ureterogram, this does not necessarily mean that the pelvis and ureter function normally. Given a moderate ureteral dilatation or a low lying kidney with ureteral displacement; this does not necessarily mean ureteral incompetency. Case 8 (figs. 9, 10 and 11) demonstrates that manometric tracing depicted the state of the ureter more accurately than did the pyelo-ureterogram.

The disturbances of ureteral function and the degree of same appear to be accurately shown by the manometric tracings, and frequently long before the changes would be obvious enough to be discovered on the x-ray plates. That the manometric observations represent the actual condition of the ureter has been corroborated, in some instances when it was possible, by the gross and microscopic examination of the specimen, and in other instances by the pyelo-ureterographic observations.

The tracings have been of aid in the interpretation of the studies made following injections of opaque solution, and in deciding which side to pyelograph when there appears to be no difference on either side from the various other examinations.

CONCLUSIONS

1. A more sensitive instrument, which is adaptable to the clinic as well as to the experimental laboratory, is presented for the recording of ureteral peristalsis.

2. The ureter possesses two chief types of contractions, the waves of which assume various configurations. There are also tonus variations and changes of rhythm.

3. The rôle of congestion of the female ureter in simple ureteritis is discussed.

4. Manometric tracings have been taken in the following conditions: (*a*) normal; (*b*) hydro-ureter and hydronephrosis; (*c*) lithiasis; (*d*) after uretero-lithotomy, and after the spontaneous passage of ureteral stone; (*e*) cord bladder; (*f*) bilateral complete duplication of ureters-simultaneous records of all ureters, and (*g*) ureteritis of various degress: tuberculous and nontuberculous.

5. Manometric tracings are of clinical value in detecting early as well as late disturbances of ureteral function; in the assistance in the diagnosis of dilated ureter and pelvis without opaque studies, or to supplement the latter; in deciding which ureter to inject with opaque solution when there appears to be no difference on both sides from the various other examinations; in knowing whether the ureter is involved in tuberculosis, calculous disease, tumor, etc.

6. The manometric tracings allow classification of ureteritis into three varieties according to the degree of ureteral activity.

7. That the manometric tracings represent the actual conditions of the ureter has been confirmed in some instances by the gross and microscopic examination of the specimen and in other instances by plates made following injections with opaque solution.

8. Relief of symptoms in patients who have ureteritis or ureteropyelitis appears to occur simultaneously with the recovery of ureteral activity. Aggravation of the disease, however, seems to be concomitant either with ureteral hyperactivity or with the loss of peristaltic contractile ability.

9. Mechanical ureteral obstruction cannot be dissociated from functional ureteral impairment, but there may be loss of function in the absence of mechanical interference.

10. The impression that the method is completely efficient in diagnosis should not be obtained. It is intended as an additional aid, and I hope that as the polygraph and electrocardiograph have been valuable adjuncts in the study of circulatory disturbances, so the recording of ureteral peristalsis will prove to be a useful and valuable method in the study and diagnosis of renal pelvic and ureteral disease.

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ABSTRACT OF DISCUSSION

DR. W. F. BRAASCH, Rochester, Minn.: The physiologic studies which were made of the ureter by Dr. Trattner are exceedingly interesting and should prove to be of practical value. I am glad that my view of the atonic or inflammatory ureter which I have held many years based on clinical and urographic evidence is confirmed by recent investigations. We are realizing more and more the importance of this pathologic change in the ureter, and when present it will affect our treatment to a marked degree.

DR. PAUL W. ASCHNER, New York: Dr. Trattner's studies on the ureter will prove most important. I do not know whether he correlates his tracings with his pyelographic study. We have always given our patients indigo carmine (sodium indigolindisulphonas) and have noticed for a number of years that in a considerable number of patients with hydro-ureter and hydronephrosis there was a marked difference in the type of ejaculation from the ureter as it came out stained with the indigo carmine. We have found that on the diseased side there is much less direct ejaculation, the fluid rather seeping out. We have had one patient under observation for a number of years, who, following pregnancy, was left with a persistent, painful, dilated kidney and ureter which, on every examination, show this phenomenon. In spite of all treatment, this has persisted. In other words, evidence of disturbance of the function of ureteral musculature can be discovered by chromoscopy.

THE EFFECT OF SOLUTIONS OF PITUITARY AND VARIOUS DRUGS ON THE MOVEMENTS OF THE SMALL INTESTINE DURING SIMPLE MECHANICAL OBSTRUCTION *

C. A. McINTOSH, M.D.
William Stewart Halsted Fellow in Surgery
AND
J. C. OWINGS, M.D.
BALTIMORE

While investigating the degree of intra-intestinal pressure in simple obstruction,[1] a method was employed which was thought to give a fairly exact conception of the type and magnitude of the intestinal motility. The degree of pressure was found to be maintained at a level (from 6 to 8 cm. of water) about twice that of the normal maximum (from 2 to 4 cm. of water), and when the intestine became active, the pressure rose to ten or fifteen times the normal (from 30 to 60 cm. of water). Having determined the type of motor activity and the degree of intra-intestinal pressure in this condition, it was concluded to record the effect of certain tissue extracts and drugs on the movements of obstructed intestine and on the intra-intestinal pressure..

For the most part, the action of a drug on smooth muscle, such as is found in the intestine, is usually determined by a suspension of a slip of that muscle in a water-bath and the addition of the drug to the medium. Perhaps the best example of this is in the biologic assay of solution of pituitary when the suspended uterus of a virgin guinea-pig is employed. In such studies it must be appreciated that certain factors and abnormalities are introduced which either are not present or might materially alter the effect of the same drug on that tissue when it is given to the living animal. Some of these factors are the contents of the medium, changes in temperature, acid-base equilibrium, the approach of the drug to the tissue, nervous control, both local and central, and nutritional abnormalities. Experiments that are conducted on a living animal eliminate many of these abnormalities, and perhaps the practical value and extent of activity of any drug or tissue

* From the Department of Surgery, Hunterian Laboratory, The Johns Hopkins University.

* This work was aided by a grant from the Hartley Corporation.

1. Owings, J. C.; McIntosh, C. A.; Stone, H. B., and Weinberg, J. A.: Intra-Intestinal Pressure in Obstruction, Arch. Surg. **17**:507 (Sept.) 1928.

extract may be more truthfully observed. Again, a correction must occasionally be made for species, and in this connection it must be stated that all the following observations were made on the dog.

Other methods of determining the motor response of the intestine to certain drugs have been by means of x-ray, direct observation of the exposed intestine, the rubber balloon method and by alteration in the rate of discharge of the intestinal contents. In all of these methods some degree of error is introduced, and each has its limitations; so, too, in the method to be described certain abnormalities are introduced and difficulties encountered. These, in the main, will be found to consist of the following: the necessity of inducing a simple mechanical intestinal obstruction, which necessitates an anesthetic and laparotomy, and the introduction of a foreign body into the lumen of the intestine. On the other hand, one is eventually able to procure what we consider good graphic records of the intestinal motility, while the degree of intra-intestinal pressure may be ascertained with a fair degree of accuracy.

The method of preparing the animals for these observations has been already described, but a repetition may be given here in brief.

TECHNIC

All animals were given ¼ grain (0.016 Gm.) of morphine hypodermically and ether anesthesia before operation. In some instances procaine, 2 per cent, was used locally. Strict aseptic precautions were employed. The bowel was doubly clamped about 6 inches (15.2 cm.) above the ileocecal valve and cut across. The lower end was turned in by the Parker-Kerr method and reinforced by a double row of mattress sutures. The clamp was removed from the proximal portion of the bowel and its lumen opened, into which was placed the following apparatus: It consisted of a brass tube about 2 inches (5.08 cm.) long, with an internal diameter of 3 mm. and a threaded external surface. A concave metal disk about 1.5 cm. in diameter was fixed at one end and a rubber washer placed over the disk. A small incision was then made in the wall of the bowel about 2 inches (5.08 cm.) proximal to the site of section. The free end of the tube was placed within the lumen of the intestine and brought out through the small incision. The disk fixed one end of the tube within the intestine. The end of the bowel was then closed in the same manner as was the distal portion. A piece of omentum was then placed over the tube, another rubber washer applied and a second concave metal disk screwed down over the whole, fixing the omentum and the wall of the bowel not too tightly, between the two rubber washers. A short rubber tube was then attached to the end of the metal tube and brought out through the abdominal wall by a separate stab incision. A small metal clamp closed the rubber tube.

Following this procedure, after from twenty-four to forty-eight hours, the rubber tube is joined through a piece of glass tubing 3 mm. in diameter to a recording mercury manometer and by a T-tube to a water manometer. The metal clamp is released, which permits the intra-intestinal pressure to be transmitted to each manometer and through the mercury one to the kymograph.

By this time the effects of the anesthetic have passed off for the most part, and a good amount of fluid matter has accumulated in the proximal portion of the obstructed bowel, so that a rather characteristic and uniform record of the motor activity of the bowel can be obtained. At any time after this until the death of the animal, drugs may be given by subcutaneous, intramuscular or intravenous injection, and the effects noted not only on the motor activity of the obstructed intestine but also on the degree of tension within the lumen of the bowel, which is comparable to the muscular activity.

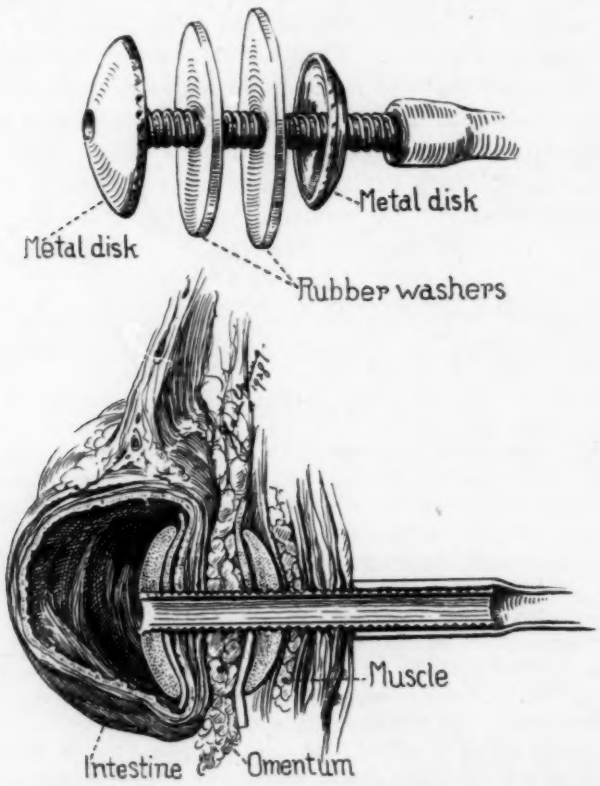

Fig. 1.—Drawing of the apparatus described in the technic is shown above; that of a cross-section of the apparatus is shown below.

By this method a number of observations have been made on those drugs and tissue extracts which activate smooth muscle or which have a specific exotocic action. Our studies have so far been confined to the action of solution of pituitary obtained from the posterior lobe (including vasopressin and oxytocin), eserine, hypertonic salt solution, ergotamine and pilocarpine.

In all the experiments we have conducted, injections have been given and all the records obtained with the animals unanesthetized and unrestrained.

SOLUTION OF PITUITARY

Ever since the demonstration by Oliver and Schafer,[2] in 1895, of the striking physiologic properties of extracts of the pituitary body, attempts to determine the presence of one or many principles and their specific physiologic rôle have been the objectives of many investigators. So far as the effects of solution of pituitary on smooth muscle in general and that of the alimentary tract in particular are concerned, the conclusions of Dale,[3] in 1909, are the first of any importance. At that time he stated that "the action of extracts of the posterior lobe of the pituitary body is a direct stimulation of involuntary muscle, without any relation to innervation," and also that the plain muscular coats of the intestines contract, but that their sensitiveness thereto is small in comparison to that of some other organs. Ever since that time, and strengthened by the experimental demonstrations and clinical use by Blair Bell [4] and his associates, the prevailing belief has been that extracts of the posterior lobe of the pituitary bring about increased intestinal motility and tone. On a more careful investigation of the literature, however, we find that experimental studies are not all in accord with this conception, and that while some believe that the extract acts as a stimulant, others say that there is a relaxation or no action.

Among those who have confirmed the stimulating effect noted by the earlier observers are Foderà and Pittau,[5] who also in 1909 found the same response as Blair Bell, that actual defecation followed injections of the extract. Ott and Scott,[6] using the rubber balloon method, noted a stimulative response that obtained the same results from extracts of many other tissues. In 1914, Guggenheim [7] brought forward evidence that the pituitary stimulant of intestinal muscle is not destroyed on boiling with alkali, as are the pressor and oxytocic principles. Young [8] observed that while alcoholic extract did not have any action on the isolated intestine of the cat, watery extract raised the tone and caused the development of large tonus oscillations. Roth,[9] in 1917, stated that solutions of pituitary contract the intestine of the rabbit without exception, and when relaxation occurred, this effect was due to the presence of chloretone in such extracts. Houssay [10] and Zondek [11]

2. Oliver and Schafer: J. Physiol. **18**:277, 1895.
3. Dale, H. H.: Biochem. J. **4**:427, 1909.
4. Blair Bell: Brit. M. J. **2**:1609, 1909.
5. Foderà and Pittau: Pathológica. **1**:269, 1909.
6. Ott and Scott: Am. Med. **6**:154, 1911.
7. Guggenheim: Biochem. Ztschr. **65**:189, 1914.
8. Young: Quart. J. Exper. Physiol. **8**:347, 1915.
9. Roth: U. S. Public Health Serv., Hyg. Lab. Bull., 1917, no. 109.
10. Houssay, quoted by Geiling: Physiol. Rev. **6**:62, 1926.
11. Zondek, quoted by Geiling: Physiol. Rev. **6**:62, 1926.

confirm these same observations. Degener,[12] in investigating the effect of died on the hypophysis of the albino rat, maintained that while the nervous portion causes a relaxation of the isolated intestinal slip, the glandular portion causes a contraction, and while the whole gland gives chiefly relaxation, after feeding with oatmeal and a vegetable diet, the total extract from the hypophysis causes contraction. Uno,[13] also working with albino rats, found that extract of the hypophysis, after the animals had been fighting for from one to six hours, caused a contraction of the intestinal slip as contrasted with the extract from the control gland, which gave relaxation. Dixon,[14] working on cats and dogs, noted that injections of solution of pituitary increase the tone of the small intestine but decrease the tone in the large bowel.

Perhaps the first observation of a typical inhibitory response of isolated intestine to solution of pituitary was made by Bayer and Peter,[15] in 1911, while working with pituitrin prepared by the Parke, Davis Company. They also sometimes observed increased activity after the period of inhibition. It must be borne in mind, too, that Blair Bell, in 1909, in testing suspended loops of intestine in Ringer's solution, found that the addition of infundibular extracts caused a relaxation and cessation of movement, but that often this was preceded by a powerful contraction.

In 1916, Shamoff[16] found that certain preparations from the posterior lobe resemble extracts of the suprarenal medulla in that they produce relaxation of the isolated intestinal loop and inhibition of its rhythmic contractions. Hoskins[17] observed relaxation of the dog's intestines when pituitrin was injected intravenously. Pancoast and Hopkins[18] made x-ray studies of eleven patients after giving pituitrin. They reported a primary depressing influence in the stomach on peristalsis, motility or both, followed by an increase of both. In the small intestine the motility, as a rule, was not affected or was slightly delayed. In the large bowel little if any effect was noted.

Atwell and Marinus[19] observed an inhibition of the intestinal rhythm of the isolated intestinal segment of the rabbit by rather weak dilutions of solutions of pituitary. Strong solutions, they stated, increase the activity.

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12. Degener: Am. J. Physiol. **60**:118, 1922.
13. Uno: Am. J. Physiol. **61**:208, 1922.
14. Dixon: J. Physiol. **57**:136, 1923.
15. Bayer and Peter: Arch. f. exper. Path. u. Pharmakol. **64**:204, 1911.
16. Shamoff: Am. J. Physiol. **39**:268, 1916.
17. Hoskins, R. G.: Pituitary Extract, J. A. M. A. **66**:733 (March 4) 1916.
18. Pancoast and Hopkins: New York M. J. **105**:289, 1917.
19. Atwell and Marinus: Am. J. Physiol. **47**:76, 1918.

Recently, McDonald [20] threw great doubt on the commonly held view that the pituitary gland contains a general stimulant of plain muscle fibers. He believes that solutions of pituitary vary greatly in their content of intestinal stimulant; that this intestinal stimulant is alcohol-soluble and alkali-stable, and that the pituitary gland is not essentially richer in the stimulant than are several other tissues.

The studies that we have made on the effects of solution of pituitary on the intestinal motility have been carried on for the most part with one preparation. The powder from which this pituitary liquid was made was prepared according to the directions given in the tenth revision of the U. S. P. except that it was subjected to an additional seventy-two hour extraction with absolute alcohol in a Soxhlet apparatus. The solution, containing 5 mg. of powder per cubic centimeter, was made up freshly each day. The additional extraction was done in the laboratory of the pharmacological department of the Johns Hopkins University School of Medicine and the solution made through the kindness of Dr. Geiling.

A number of tests were made with pituitrin prepared by the Parke, Davis Company, and the effects of this drug, so far as intestinal motility is concerned, are identical with those procured when our own freshly made pituitary fluid was used.

As already mentioned, a good record of the intestinal motility may be procured by the foregoing method from thirty-six to forty-eight hours following the establishment of simple obstruction. Any time after this, injections of pituitary fluid may be given, intravenously and intramuscularly, and the results noted. Coincident with the effects seen on the motility of the bowel, certain general constitutional reactions were observed that in a sense confirmed that the extract was active. These in the main consisted of a marked slowing of the pulse rate and respirations, an extreme degree of blanching of the skin and mucous membranes; if the dose was sufficiently large, the animal became "knocked out" as it were, and lay extremely still if it had been active previously. These responses following intravenous injection came on instantaneously, while after intramuscular injections, the constitutional responses were delayed from three to ten minutes.

As will be seen in the accompanying tables, the doses varied from 0.025 to 1 cc., the former being about as small an amount as could be given and still furnish positive and definite general effects. In every instance, as shown by a large number of graphic records, the response of the obstructed small intestine was the same. Whether the bowel was in an extreme state of motor activity, either spontaneous or induced, as the result of stimulation from some drug such as eserine, or whether the intestines were inactive, as would be shown by a straight

20. McDonald: Quart. J. Exper. Physiol. **15**:191, 1925.

line on the tracings, not one instance of increased motor activity was found. In every case, the graphic record is a straight line that tends to approach the base line, indicating a falling off of intra-intestinal pressure and tone, and the absence of motor activity. The duration of these effects is dependent on the quantity of pituitary fluid given. The largest doses, 0.5 or 1 cc., are effective for from twenty to thirty minutes, while the smaller ones, 0.025 or 0.05, act for only from five to ten minutes at the most. The general constitutional reaction seems to go hand in hand with the effect on the obstructed intestine. When the one has passed off and is finished, the other, too, is returned practically to the same condition as before the injection. Or if the effects of the drug are delayed, as following the intramuscular injection, in the same way the response in the bowel occurs at the same time as the general reaction.

In a few instances, it has been possible to observe intense peristaltic activity through a thin and scaphoid abdomen. When this was the case, or when the same could be induced by giving eserine, and much gurgling could be heard, the giving of a moderate quantity of pituitary fluid would cause a disappearance of the visible peristalsis and a cessation of the noises.

Besides pituitary fluid and pituitrin, we have tried the effect of two other extracts of the posterior lobe of the pituitary gland, known as vasopressin and oxytocin. These preparations were procured from a batch that had been sent out by the Parke, Davis Company for clinical use and experimental trial. Kamm [21] and others have indicated their method of preparation and have brought forward good evidence to show that these substances represent two principles that are present in the posterior lobe of the hypophysis.

Though, as is shown in table 1, we have made only five injections, three with oxytocin and two with vasopressin, we have noted practically the same results as we have experienced with solution of pituitary and pituitrin, except for the following differences: The vasopressin would appear to possess a pressor substance in much greater concentration than in pituitary fluid, pituitrin or oxytocin, for an intravenous injection of 0.25 cc. caused an extreme blanching of the mucous membranes and fall in the pulse rate that were much more marked than was ever noted with 1 cc. of the other substances. Oxytocin gave the same constitutional reaction and effect on the intestinal motility as did pituitary fluid or pituitrin.

As such a constant and definite result was observed after each injection of pituitary fluid, and this contrary to what was considered

21. Kamm, Aldrich, Grote, Rowe and Bugbee: J. Am. Chem. Soc. **1**:573, 1928.

TABLE 1.—*Effect of Pituitary Fluid and Pituitary on Intra-Intestinal Pressure During Obstruction of the Small Bowel; Comcomitant Systemic Effects*

Dog					Maximal Intra-Intestinal Pressure, Cm. Water		Pulse Rate			
Series Number	Hours Obstructed	Drug	Quantity, Cc.	Method of Injection	Before	After	Before	After	Pallor of Mucous Membrane	Duration of Effect, Minutes
OP 27	0	Pituitary	1	Intravenously	2-4	2-4	100	60	Extreme	25
OP 27	72	Pituitary	1	Intravenously	2-5	2-5	...	...	Extreme	20
OP 27	136	Pituitary	1	Intravenously	114	6-8	200	120	Extreme	25
OP 28	24	Pituitary	1	Intravenously	6-8	2-4	...	...	Extreme	20
OP 28	73	Pituitary fluid	1	Intravenously	2-4	2-4	...	...	Extreme	20
OP 29	21	Pituitary fluid	1	Intravenously	14	2-4	...	...	Extreme	15
OP 29	4	Pituitary	1	Intravenously	8-10	2-4	...	...	Extreme	20
OP 33	31	Pituitary	1	Intramuscularly	18-20	2-4	100	60	Marked	50
OP 33	72	Pituitary fluid	1	Intravenously	28	4-6	...	...	Extreme	20
OP 33	76	Pituitary	1	Intramuscularly	18	2-4	108	68	Moderate	50
OP 34	30	Pituitary	1	Intravenously	32	4-6	...	...	Extreme	20
OP 34	68	Pituitary fluid	1	Intramuscularly	48	2-4	120	84	Moderate	15
OP 34	76	Pituitary	1	Intramuscularly	24	4-6	110	72	Moderate	25
OP 27	124	Pituitary fluid	0.5	Intravenously	30	2-4	...	...	Marked	25
OP 27	136	Pituitary fluid	0.5	Intravenously	8-10	2-4	200	120	Marked	20
OP 27	137	Pituitary fluid	0.5	Intravenously	18	2-4	200	120	Marked	20
OP 33	45	Pituitary fluid	0.5	Intramuscularly	4-6	2-4	128	80	Moderate	20
OP 33	60	Pituitary fluid	0.5	Intravenously	34	4-6	...	...	Marked	20
OP 34	48	Pituitary fluid	0.5	Intramuscularly	18	6-8	124	68	Moderate	20
OP 34	56	Pituitary fluid	0.5	Intravenously	10-12	2-4	120	72	Marked	15
OP 34	56½	Pituitary fluid	0.5	Intramuscularly	18-20	2-4	124	84	Moderate	15
OP 33	56	Pituitary fluid	0.25	Intravenously	20	12	...	...	Moderate	30
OP 34	43	Pituitary fluid	0.25	Intravenously	25	6-8	...	...	Moderate	10
OP 33	96	Pituitary fluid	0.1	Intravenously	20	4-6	110	60	Moderate	12
OP 34	130	Pituitary fluid	0.1	Intravenously	10-12	2-4	130	68	Moderate	10
OP 34	136	Pituitary fluid	0.1	Intravenously	26	5-6	168	84	Moderate	10
OP 34	149	Pituitary fluid	0.1	Intravenously	6-8	4-6	...	...	Moderate	5
OP 33	120	Pituitary fluid	0.05	Intravenously	10-12	6-8	120	96	Slight	10
OP 33	120½	Pituitary fluid	0.05	Intravenously	10-12	6-8	128	72	Slight	10
OP 33	121	Pituitary fluid	0.05	Intravenously	10-12	6-8	108	66	Slight	15
OP 34	136	Pituitary fluid	0.05	Intravenously	48	8-10	168	84	Slight	5
OP 34	136½	Pituitary fluid	0.05	Intravenously	5-6	5-6	168	92	Slight	10
OP 33	144	Pituitary fluid	0.025	Intravenously	18-20	6-8	140	76	Slight	5
OP 33	144½	Pituitary fluid	0.025	Intravenously	16-18	2-4	128	72	Slight	5
OP 33	168	Pituitary fluid	0.025	Intravenously	10	5	148	96	Slight	5
OP 34	144	Pituitary fluid	0.025	Intravenously	4-6	6-8	180	112	Slight	5
OP 34	144½	Pituitary fluid	0.025	Intravenously	14-16	10-12	148	108	Slight	5
OP 34	149	Pituitary fluid	0.025	Intravenously	36-40	6-8	...	...	Slight	4

TABLE 1.—*Effect of Pituitary Fluid and Pituitary on Intra-Intestinal Pressure During Obstruction of the Small Bowel; Concomitant Systemic Effects—Continued*

Dog					Maximal Intra-Intestinal Pressure, Cm. Water		Pulse Rate			
Series Number	Hours Obstructed	Drug	Quantity, Cc.	Method of Injection	Before	After	Before	After	Pallor of Mucous Membrane	Duration of Effect, Minutes
OP 34	166	Pituitary fluid	0.025	Intravenously	16-18	6-8	180	128	Slight	7
OP 34	167	Pituitary fluid	0.025	Intravenously	30	8-10	180	148	Slight	10
OP 34	168	Pituitary fluid	0.025	Intravenously	26-28	26-28	184	180	Slight	..
OP 33	93	Oxytocin	0.5	Intravenously	18	6-8	...	Slowing	Moderate	15
OP 36	47	Oxytocin	0.5	Intravenously	32	2-4	144	92	Marked	30+
OP 36	47½	Oxytocin	0.4	Intravenously	2-4	2-4	132	92	Marked	20+
OP 36	51	Vasopressin	0.25	Intravenously	30	4-6	132	56	Extreme	50
OP 36	52	Vasopressin	0.25	Intravenously	3-4	3-4	120	64	Extreme	20+

the general belief concerning the mode and manner of action of this substance, we attempted a few experiments to determine the action of pituitrin and solution of pituitary on the isolated strip of a dog's intestine. In selecting portions of bowel for these studies, we have been well aware of the variety of conditions to which they were subjected. For example, we have used portions of intestine that have been obstructed from forty-eight to ninety-six hours. We have also employed bits of bowel that were procured from dogs that died almost instantaneously from thoracotomy and bleeding. Practically all the material obtained in this manner was kept, after thorough washing, in freshly made Locke's solution according to the modification of Smith and McClosky.[22] In other cases, absolutely fresh material was cut off as required from the intestine of an animal kept under iso-amyl-ethyl anesthesia, thus preventing any fall in temperature. Added to these variations, the slips of muscle suspended were cut in some cases longitudinally and in others transversely, in order to determine the effect on both types of muscle fiber.

The slips of muscle that were procured under these many and varied conditions were suspended in the usual manner in 100 cc. of freshly made Locke's solution, provided with an adequate supply of oxygen and kept at a constant temperature of 37 C. by a surrounding water-bath. The ordinary lever and kymograph completed the equipment.

The quantities of pituitary fluid, pituitrin and oxytocin added to the medium in which the muscle slips were suspended varied from 0.05 to 5 cc.; that is, from 0.25 to 25 mg. per cent of dry powder. In all instances, with the exception of two cases, and there were close

22. Smith and McClosky: U. S. Public Health Serv., Hyg. Lab. Bull., 1924, no. 138.

to one hundred fresh preparations, we found no stimulation, a fall in the tone or a cessation of the rhythmic movements. In the one there was a cessation of the rhythmic movements and a slight rise in the tone. In the other, a questionable stimulation occurred; that is, a slight increase in the height of one of the rhythmic waves was recorded, though from its appearance it would not seem unusual if

Fig. 2 (O. P. 33).—Record for dog obstructed for sixty-eight hours. The uppermost tracing is the normal with maximum pressure of 27 cm. of water; the second tracing was made following the injection of 1 cc. of pituitary fluid intravenously. The cessation of waves and the fall of pressure to 3 cm. of water should be noted. The lowest record shows a return of peristalsis after twenty-three minutes. A rise in the intra-intestinal pressure is represented in all the tracings by a descent of the graph toward the bottom of the record. The timer records every sixth second.

Fig. 3 (O. P. 34).—Record for dog obstructed for fifty-five hours. The top tracing shows the normal; the second, the effect of 0.5 cc. of pituitary fluid given intravenously. The third shows the return of motor activity after fifteen minutes when 0.5 cc. was given intramuscularly.

pituitary had not been added to the medium. The accompanying tracings show in a general way the results obtained.

Repeated doses of pituitary fluid or pituitrin in the animal with intestinal obstruction caused the same general constitutional reactions and the same effect in the intestinal motility as did the first injection,

though its duration is somewhat shorter and not so pronounced, provided the quantity employed is the same in each instance. With small doses, still sufficient to give a constitutional effect, the repetition does not bring about continued inhibition of the intestinal motor activity, though certain constitutional effects still recur.

ESERINE

The action of eserine sulphate, as it is stated in the standard texts on pharmacology (Cushny,[23] Meyer and Gottlieb,[24] Poulsson[25] and others) is that of stimulation of both smooth and voluntary muscles either through their motor end-plates or through the production of a hypersensitivity of these same structures. Its employment, then, as a stimulant of bowel musculature is to be expected. Martzloff,[26] using the small dosage of 1/100 grain (0.00065 Gm.) together with 1/40 grain (0.0016 Gm.) of strychnine, reported that the clinical use of this

Fig. 4 (O. P. 34).—Record for dog obstructed for forty-three hours. The top tracing shows the normal, reaching a maximal intra-intestinal pressure of 24 cm. of water; the second tracing shows the effect of 0.25 cc. of pituitary fluid given intravenously. The bowel was inactive for ten minutes.

drug in the prevention of distention, and other conditions, was far from satisfactory. Martin and Weiss,[27] on the other hand, employing a much larger dose, from 1/16 to 1/20 grain (0.004 to 0.003 Gm.) of physostigmine salycilate, found satisfactory and beneficial results in those cases with a nontoxic type of distention. It was found less

23. Cushny: A Text Book of Pharmacology and Therapeutics, ed. 8, Philadelphia, Lea & Febiger, 1924.

24. Meyer and Gottlieb: Experimental Pharmacology as a Basis for Therapeutics, ed. 2, Philadelphia, J. B. Lippincott Co., 1926.

25. Poulsson: A Text Book of Pharmacology and Therapeutics, Baltimore, Williams & Wilkins Company, 1924.

26. Martzloff: Bull. Johns Hopkins Hosp. **35**:370, 1924.

27. Martin, H. E., and Weiss, S.: Use of Physostigmine in Abdominal Distention, J. A. M. A. **84**:1407 (May 9) 1925.

useful in the treatment of toxic abdominal distention, so-called. Bartlett,[28] too, found the employment of a dosage of 1/25 grain (0.002 Gm.) to give beneficial effects.

Cross [29] also advocated the use of the drug clinically combined with alternating doses of solution of pituitary, and at the same time gave experimental proof of his conviction by suspending a portion of the human appendix in Locke's solution and adding eserine and solution of pituitary, alternately. A stimulative effect is observed that is greatly

Fig. 5 (O. P. 34).—Record for dog obstructed for 165 hours. The top tracing shows a normal record; the second shows the effect of 0.025 cc. of pituitary fluid given intravenously. The third reveals that a repetition of the same dose does not produce any effect.

Fig. 6 (O. P. 36).—Record for dog obstructed for forty-eight hours. The normal tracing was for twenty minutes with maximum pressure of 32 cm. of water. The second tracing shows the effect of 0.5 cc. of oxytocin given intravenously, and the third of 0.4 cc. given intravenously twenty minutes later. The pressure was 5 cm. of water.

augmented by the addition of the second drug, no matter whether the eserine or the solution of pituitary is first employed.

28. Bartlett: After-Treatment of Surgical Patients, St. Louis, C. V. Mosby Company, 1918, p. 128.

29. Cross: Brit. M. J. 1:9, 1924.

The dose that we have administered was either 1/50 or 1/150 grain (0.001 or 0.0004), given for the most part intramuscularly. The only intravenous injections were made when 1/150 grain was used, all of which resulted in a definite increase in the intestinal motility except on one occasion when only a slight stimulative effect was noted. Following the intramuscular injections of 1/50 grain, there was a period of fifteen minutes, corresponding to the period of absorption, during which the intestines pursued their usual activity. A gradual rise in the intra-intestinal pressure then occurred, with subsequent abrupt increments, followed by a drop that was less in extent than the preceding rise until the pressure reached well above 100 cm. of water. This is much greater than is experienced in animals that have not been subjected to such stimulation, when it is rare to encounter a pressure greater than 50 cm. This period of increased intestinal motility continues for at least thirty minutes and may last an hour or even longer, though the usual duration is forty-five minutes. As

Fig. 7 (O. P. 36).—Record for dog obstructed for fifty-two hours. The normal motor activity is shown at the beginning of the second tracing when the pressure maximum is 30 cm. of water. After 0.25 cc. of vasopressin was injected intravenously there was little activity and none during the third tracing. The pressure was from 4 to 6 cm.

TABLE 2.—*Effect of Eserine Sulphate on Intra-Intestinal Pressure During Obstruction of the Small Bowel*

Dog					Maximal Intra-Intestinal Pressure, Cm. Water		Duration of Effect, Minutes
Serial Number	Hours Obstructed	Drug	Quantity, Grain	Method of Injection	Before	After	
OP 27	25	Eserine	1/50	Intramuscularly	2-4	100+	25+
OP 27	31	Eserine	1/150	Intravenously	6	6-8	10
OP 27	31½	Eserine	1/150	Intravenously	6-8	28	10
OP 32	32	Eserine	1/150	Intramuscularly	6-8	42	15
OP 27	50	Eserine	1/150	Intravenously	10-12	100	30
OP 27	53	Eserine	1/50	Intramuscularly	8-10	95	40
OP 27	73	Eserine	1/50	Intramuscularly	2-5	105	30
OP 27	100	Eserine	1/50	Intramuscularly	10	80	40
OP 27	138	Eserine	1/50	Intramuscularly	6-8	114	15+
OP 28	25	Eserine	1/50	Intramuscularly	2-4	26	30
OP 29	22	Eserine	1/50	Intramuscularly	6-8	32	20+
OP 33	92	Eserine	1/50	Intramuscularly	44	60	50
OP 34	77	Eserine	1/50	Intramuscularly	6-8	58	70

might be reasonably expected, the smaller doses have a correspondingly shorter period of effectivity. The figures followed by a plus sign in table 2 under the heading "Duration of Effect" do not represent the true period of action in all probability. At these times either another counteracting drug was injected, or the tracings and observations were discontinued.

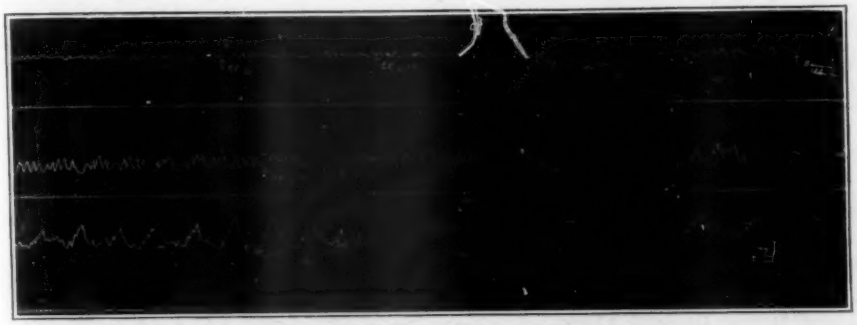

Fig. 8.—Fresh longitudinal sections of dog's intestine cut from a normal animal under amytal anesthesia. The uppermost tracing shows the effect of 0.05, 0.2 and 5 cc. of pituitary fluid; the middle tracing shows the effect of 0.1 and 2 cc. and the lowest tracing shows the effect of 0.2 and 1 cc.

Fig. 9.—Effect of 0.5, 1 and 2 cc. of pituitary fluid in longitudinally suspended portions of a dog's intestine that had been obstructed 100 hours.

Corresponding to the solutions of pituitary there are also definite constitutional or general systemic responses. The chief of these is a twitching of peripheral skeletal muscle. This effect, in some instances, is violent. The other obvious physiologic responses were contraction of the pupil, salivation, slowing of the pulse and occasional vomiting. On two occasions pituitary fluid was given before the injection of eserine. In these instances, the muscle twitchings were much less and the intestinal motility not so violent and more normal in type.

HYPERTONIC SODIUM CHLORIDE

Among the first investigators to emphasize the value of sodium chloride in intestinal obstruction were Hartwell and Hoguet.[30] These workers found that the giving of physiologic sodium chloride solution to dogs with duodenal obstruction increased their life from a few days to about three weeks. In 1920, MacCallum and others [31] also noted that a large supply of chlorides prevented the symptoms of pyloric obstruction and restored the plasma chlorides to their proper level. Haden and Orr [32] were the first to investigate in detail the changes in the blood chemistry, which they found were most marked in high intestinal obstruction. To dogs they gave 50 cc. of a 10 per cent solution of sodium chloride with good results, but had animals live twenty-one and twenty-eight days when they gave 500 cc. of a 0.85 per cent solution daily. In one instance, the animal died soon after

Fig. 10 (O. P. 27).—Record for dog obstructed for seventy-six hours. The arrow on the upper tracing shows the effect of 1/60 grain (0.0013 Gm.) of eserine sulphate given intramuscularly. Note the intestinal activity after fifteen minutes and still present at the end of the tracing, thirty-five minutes. The intra-intestinal pressure reached a maximum of 106 cm. of water.

an injection of a 25 per cent solution. Hughson and Scarff [33] were able to show experimentally that hypertonic salt solution not only prevents absorption from the intestine but also stimulates peristalsis, while its use in two clinical cases of paralytic ileus proved a great success after pituitary had failed completely. Ross,[34] also, both experi-

30. Hartwell, J. A., and Hoguet, J. P.: Experimental Intestinal Obstruction in Dogs with Especial Reference to the Cause of Death and the Treatment by Large Amounts of Normal Saline Solution, J. A. M. A. **59**:82 (July 13) 1912.

31. MacCallum, Linty, Vermilego, Lyett and Boas: Bull. Johns Hopkins Hosp. **31**:1, 1920.

32. Haden and Orr: Bull. Johns Hopkins Hosp. **24**:26, 1923; J. Exper. Med. **38**:55, 1923; Surg. Gynec. Obst. **37**:465, 1923.

33. Hughson and Scarff: Bull. Johns Hopkins Hosp. **35**:197, 1924.

34. Ross: Canad. M. A. J. **16**:241, 1926.

mentally and clinically found hypertonic saline a great intestinal stimulant. Coleman,[35] in a review of his cases, found that the giving of 3 quarts of a 3 per cent solution reduced the mortality from 50 to 11.1 per cent.

In our studies we gave intravenously either 5 or 10 cc. of a 25 per cent solution. In all but one instance, we found a stimulative response. Generally, not only is there a rise in the intestinal tone, as is shown by an increase in the average rise of the intra-intestinal

Fig. 11 (O. P. 27).—Record for dog obstructed for 132 hours, showing the effect of 1/50 grain (0.0013 Gm.) of eserine sulphate given intramuscularly. The intra-intestinal pressure had reached 114 cm. of water when 1 cc. of pituitary fluid was given intravenously. Note the marked cessation of movement and the fall in pressure.

Fig. 12 (O. P. 34).—Record for dog obstructed for seventy-eight hours. The upper tracing shows a late effect (30 to 50 minutes) after 1 cc. of pituitary prepared by Park, Davis Company was injected. The lower tracing shows the effect of 1/50 grain (0.0013 Gm.) of eserine intramuscularly in the same dog fifteen minutes later. Note that the muscular activity is not so great as usually occurs after administration of eserine.

pressure, but the maximum levels are well above the normal. The duration of activity is generally about from twenty to thirty minutes. The motor activity is not so violent as after the administration of

35. Coleman, E. P.: Use of Hypertonic Saline Solution in Acute Intestinal Obstruction, J. A. M. A. **88**:1060 (April 2) 1927.

TABLE 3.—*Effect of Hypertonic Sodium Chloride on Intra-Intestinal Pressure During Obstruction of the Small Bowel*

Dog					Maximal Intra-Intestinal Pressure, Cm. Water		
Serial Number	Hours Obstructed	Sodium Chloride, per Cent	Quantity, Cc.	Method of Injection	Before	After	Duration of Effect, Minutes
OP 27	48	25	5	Intravenously	14-16	28	10
OP 27	49	25	5	Intravenously	6	18	20
OP 27	136	25	10	Intravenously	2-4	19	30
OP 28	7	25	10	Intravenously	2-4	2-4	..
OP 28	29	25	10	Intravenously	2-4	26	10
OP 29	22	25	10	Intravenously	2-4	32	20
OP 33	77	25	10	Intravenously	2-4	54	25
OP 33	96	25	10	Intravenously	30	36	30
OP 34	106	25	10	Intravenously	10	70	30
OP 34	137	25	10	Intravenously	5-6	58	25+

eserine, and the type of graph has the appearance of an increase in the normal rather than the changed character to the tracing obtained from eserine. In other words, the same rhythmic activity is found

Fig. 13 (O. P. 34).—Record for dog obstructed for 120 hours, showing the stimulative action of 10 cc. of 25 per cent sodium chloride intravenously. The intra-intestinal pressure rose to 57 cm. of water. The lower tracing shows the result of giving 1 cc. pituitary fluid.

after hypertonic saline is given as is found normally, except that the maximum change in pressure is greater than normal.

Ergotamine and pilocarpine were also given, and though each appeared to have a slight stimulative action, the extent of the response usually was not greater than the normal.

COMMENT

We have already enumerated the chief methods that are employed to investigate the intestinal motor response to various drugs, extracts and other therapeutic agents. In each it is easy to find when error is introduced, so that the employment of a new method, even though it does introduce new difficulties, is more or less justified so long as it overcomes some of the old pitfalls. And not only may it enable

us to get new ideas and conceptions about an old and long studied condition, but it may also serve to show how remedial agents affect that condition when their action is investigated in a new light. Therefore, the introduction of a new method of study, we feel, is justified in order that its efficacy may be tested and the results of previous studies confirmed or disproved.

In the main, this means of determining the action of various drugs on intestinal musculature does away with those difficulties that arise in the experiments on isolated muscles, such as temperature, acid-base equilibrium and nutritional factors. The drug that is added to the medium in which the isolated slip of muscle is suspended comes in contact with the muscle through a different path from that which approaches it through the blood stream. There is no interference with any of the local or general nervous mechanisms, while all those systems and structures such as blood pressure, through which a drug may exert its influence primarily or secondarily, are intact. In a moderate degree, too, a measure of the degree of the activity of a drug or extract may be gaged by its influence on the intra-intestinal pressure which is afforded a constant graphic representation. A repeated number of observations can also be made on the same animal. Of course, it must be borne in mind that each experiment is made on a dog that is in a pathologic state which each day becomes more severe, leading to a lowered resistance, gross changes in the blood chemistry and probable metabolic disturbances. These are comparable, however, to the same conditions that exist in human beings when the need for intestinal stimulants is paramount. So that the measures employed to prepare the animal for experimental purposes, and the early and late sequelae that result therefrom, do not introduce so great a degree of error as they would appear to do at first. A further point to be considered when comparing experiments on isolated tissue with those on the intact animal is that in the latter case the normal channels are present which influence the destruction or excretion of the drug.

A final interesting observation noted during these studies was the cause of death in one dog that was given repeated doses of eserine. While, for the most part, the animals would die from a complicating peritonitis resulting from a leak about the apparatus, in this dog, which received large and repeated doses of eserine that raised the intra-intestinal pressure greatly above what it would have been had this drug not been employed, the cause of death was from a perforation of the intestine. In this animal the small intestine was greatly distended for many inches above the site of obstruction; the antimesenteric border exhibited large diamond-shaped ecchymotic areas, ulceration of the mucous membrane and a fair sized perforation. A similar condition was not found in those animals to which eserine was not given. Indeed,

it is a rare occurrence in those dogs that die from simple intestinal obstruction to find at autopsy a perforation of the intestine at the antimesenteric border.

In discussing the results obtained from the use of pituitary fluid and pituitrin, we must admit that we found these different from what we had expected, though on more careful examination of the literature, not unlike those which other investigators had reported. When one observes in one place that solution of pituitary is a stimulant of smooth muscle and in another that it relaxes a suspended slip of small intestine, the only conclusion to be drawn is that either a different extract was employed in each case or the methods of observation introduced differences that in the end resulted in different conclusions. So far as the action of the extract on the isolated muscle is concerned, a great deal has been done to show the error that is introduced by depressor substances common to many tissue extracts, and also preservatives employed in the commercial products. Changes in the P_H of the bath as a cause of relaxation of strips of intestine have recently been emphasized by Gruber.[36]

The constancy of results that we have obtained, however, associated with the constant constitutional effects that have followed the giving of pituitary fluid, intramuscularly and intravenously, convinces us that they are true. Special precautions were taken to free the powder from which the fluid was made of all depressor substances, and a preservative was not added.

A word or two must be said about the change in the intra-intestinal pressure that is shown in table 1 under maximal pressures before and after injection. As a general rule, it is seen that the pressure in the column headed "Before" shows a greater pressure than that headed "After." The interpretation of this is that just before the injection of the pituitary fluid a period of increased intestinal pressure occurred, while after the injection the pressure fell off, and the intestine was apparently inactive until the effects of the extract had worn off. In some other instances, the pressure before the injection is not greater than after it. In these cases the intestine was apparently inactive for the few minutes immediately preceding the giving of the pituitary fluid, and no stimulation resulted with the exception of a continuation of inactivity and generally a falling off of the tone. Occasionally, a great degree of pressure is noted just before the injection. In these instances eserine had been given, and while it was still active, pituitary fluid was administered, which resulted in an abrupt fall of pressure.

So far as we could determine, there was no change in the degree of activity of the intestinal musculature following injections of pituitary

36. Gruber: J. Pharmacol. & Exper. Therap. **30**:73, 1926.

fluid so far as a relationship to the duration of the obstruction was concerned. The response in a dog in which obstruction for forty-eight hours was produced was the same as that in one obstructed six or seven days. In the same way, when a terminal peritonitis set in, a change in the usual response could not be observed.

The changes in the intra-intestinal pressure were observed for from one to two hours after the giving of the pituitary fluid. After from thirty to forty-five minutes, the changes in the pulse rate and the degree of pallor of the mucous membranes would have returned to normal. The rhythmic intestinal activity would also ensue in from twenty to forty minutes as a general rule, but a degree of activity or a rise in the intra-intestinal pressure that was greater than it had been before the administration of the pituitary fluid was never observed.

It must be stated that we have no record of the action of the solution of pituitary on the large bowel, nor have we any for the experiments on the isolated intestine. It is just possible that there might be a somewhat different response in this portion of the intestinal canal which would account for the defecation observed by some investigators following the injection of solution of pituitary.

An exact explanation of how this tissue fluid acts on the intestinal canal to bring about the results just stated is rather difficult. It would appear reasonable, however, to assume that, as the action of pituitary fluid on the isolated slip of intestine was no stimulation, a fall in tone or a cessation of rhythmic movements, while in the animal there was always a cessation of movement without exception, probably besides a possible direct action on the muscle itself; there was also a second factor, possibly the anemia of the wall of the bowel due to a vasoconstriction, or some other secondary effect.

While the use of pituitary solution is strongly advocated in all cases of intestinal paresis, it has by no means a constant and adequate therapeutic value. The opinion of various clinicians might vary so far as this point is concerned, but in the light of our studies, we should not expect a return of or an increase in the peristaltic activity following the use of the pituitary fluid we have employed.

In our experience, eserine was the most effective intestinal stimulant. Both in the response of isolated intestinal muscle to this drug and in all instances in which a sufficient dosage was given to the living animal, there was observed, as was previously stated, not only a rise in the tone of the bowel, but also a great increase in the degree of motor activity.

Hypertonic sodium chloride, too, would appear to increase the intestinal motor function. We are unable to state whether the extent of this action is greater when the blood chlorides have fallen to below normal, but we do feel that the stimulative power is greater late in the

obstruction. Reference should be made here to the work of Haden and Orr,[37] who stated that ligation of the dog's ileum at the ileocecal valve is followed by little increase in the nonprotein nitrogen of the blood, no change in the blood chlorides and carbon dioxide combining power of the plasma. This being the case, then, the value and efficacy of hypertonic sodium chloride as an intestinal stimulant would not bear any relation to the percentage composition of the chlorides in the blood.

SUMMARY

1. A method of recording the movements of the small intestine and the degree of intra-intestinal pressure in simple intestinal obstruction in dogs is described.

2. The effect of various solutions of pituitary and certain drugs on the movements of the small intestine and the intra-intestinal pressure in obstruction is recorded.

3. The action of pituitary fluid, pituitary, vasopressin and oxytocin on the obstructed intestine would appear to be one of depression and slight relaxation, though the general or other systemic effects induced by these extracts may vary considerably.

4. On the isolated portion of dog's intestine, whether from normal or obstructed bowel, the effects of pituitary fluid and pituitary are those of relaxation if any change occurs.

5. In the dog with intestinal obstruction, intramuscular injections of eserine in adequate amount have a decided stimulative action on the small intestine. The rise in the intra-intestinal pressure is also great and may measure more than 100 cm. of water.

6. The value of hypertonic sodium chloride as an activator of peristalsis is proved experimentally.

37. Haden and Orr: J. Exper. Med. **37**:365, 1923.

THE DEVELOPMENT OF BONE

(A) THE PROCESS OF DEVELOPMENT IN BONES OF DIFFERENT TYPES; (B) NORMAL PHYSIOLOGIC CALCIFICATION OF THE MATRIX IN CARTILAGE AND IN BONE; (C) THE PROBLEM OF THE MANNER OF DEPOSITION OF THE CALCIUM SALTS

JAMES CRAWFORD WATT, M.D.
Associate Professor of Anatomy, University of Toronto
TORONTO

In the studies here recounted, three different aspects of the problems involved in the development of bone are discussed, as indicated in the title. All three studies are closely interwoven and cannot be considered separately without much needless repetition and reduplication. Consideration is given each aspect in its proper relation to various portions of the work to be described, and they must be considered collectively for a proper elucidation of the problems discussed and for an interpretation of the results of the work which has been accomplished.

The process of the transport of calcium salts in the body and their deposition in bone have already been discussed in previous papers. But a much more thorough, detailed and minute study has now been made of the process of calcification of the cartilaginous and bony matrix of the skeleton, and the results obtained are embodied in this paper. It is to be remembered always that this calcification is a normal, physiologic process, and the conclusions arrived at by its study are far different from those derived from an examination of the pathologic process of calcification in various other tissues. A discussion of my views on the pathologic process is contained in a paper recently published,[1] showing that calcification in this case is a physical process of precipitation into dead or injured tissues and is not a function of the tissue cells. On the contrary, in the development and growth of the skeleton it will be shown that calcification is a function of the living cells and is dependent on their activity for its occurrence.

MATERIAL

Bones in process of ossification were examined in their earliest stages by means of serial sections of young human embryos aged from 6 to 12 weeks. Formation of bone both in cartilage and in membrane was conveniently followed here, especially in the skull, without decalcifying.

Later stages were obtained by sectioning the humerus, radius, ulna, ribs and parietal bones from human fetuses of various ages from 4 to 9 months, and also

1. Watt, J. C.: Deposition of Calcium Salts in Areas of Calcification, Arch. Surg. **15**:89 (July) 1927.

similar specimens from young rats, some of which were new-born. For short and irregular shaped bones the tarsal bones of human fetuses aged from 6 to 9 months and those of children up to one month after birth were used, the navicular, cuboid, talus and calcaneus of one individual forming a set of four different stages valuable for comparisons. In these bones, ossification occurs as follows: the calcaneus in the sixth month, the talus in the seventh and the cuboid in the ninth month of intra-uterine life, and the navicular long after birth, usually in the fourth year.

TECHNIC

For the earliest stages small embryos were cut as a whole, while only the skulls of larger ones were used. For later stages, long bones were cut across the shaft so as to obtain about 5 mm. of bony shaft along with the cartilaginous epiphyses. Such a specimen was then split longitudinally and contained unaltered cartilage, calcified cartilage and newly formed bone in serial order in the section. Parietal bones were sectioned both transversely and tangentially. Tarsal bones were sectioned in their long axis, some of them serially.

All specimens were preserved in formaldehyde saline solutions and were sectioned without decalcifying so as to preserve calcium deposits intact. Duplicate specimens of some were decalcified to provide for ordinary histologic examination. All parts of the specimens remained intact on sectioning except for the hard, fully ossified shafts of long bones or the large ossified centers of some tarsal bones, which either broke somewhat or else slightly separated from the rest of the specimens at the line of junction with the calcified cartilage. Sections were cut 10 microns thick when possible, but when cutting was difficult they were made slightly thicker.

It is to be noted that there is a distinct difference in consistency between calcified cartilage and bone. Bone can be cut only with great difficulty, and only small areas of it can be gone through by the microtome knife without spoiling the sections and without danger of serious injury to the knife. Calcified cartilage is much softer and can be sectioned fairly easily.

In every case some sections were left unstained for both light and dark-field examinations, while other sections of each specimen were stained with hematoxylin and eosin and some with Mallory's triple stain.

I. PHYSIOLOGIC CALCIFICATION OF CARTILAGE PRECEDING OSSIFICATION

Preliminary to the occurrence of ossification in the skeleton there is a primary, rapid and transitory process of calcification in the cartilage about to be changed into bone. This process will be described in several different locations, and as it is best seen in the long bones formed in cartilage the conditions here will be first described.

Calcification of Cartilage in Shaft of Long Bones.—At the time when the budding blood vessels carrying osteoblasts with them invade the cartilaginous shaft of the future long bone in order to initiate ossification, the cartilage is seen to exhibit several well marked zones displaying different characteristics. These areas will be enumerated in order, passing toward the center of ossification.

At the extremities of the future bone (fig. 1, plate I), the cartilage cells are small and deeply stained and lie in a dense matrix which also

stains well. Next to this lie zones in which the cells become progressively larger and more irregular in disposition and in which the staining of the matrix becomes paler.

Succeeding this, there is an area of transition terminating in the zone in which the enlarged cartilage cells lie close together in large lacunae arranged in columns. Between the cells of a column lie thin trabeculae of cartilage, while between contiguous columns lie heavy trabeculae of matrix. The cells of this area stain irregularly, and many appear to be degenerating and dying as the line of newly forming bone is approached. The matrix of this zone is heavily calcified and stains deeply with hematoxylin.

The final area seen in the specimen is one containing the primary marrow spaces with large blood vascular sinuses separated by trabeculae of calcified cartilage. On the latter, spicules of new bone are being deposited by the osteoblasts which were brought in with the blood vessels and now line the surface of the trabeculae.

On examining the calcium deposited in such a specimen as that described, one finds that in the bony spicules it is finely granular and requires fairly high magnification to reveal its nature. The cartilage trabeculae on which bone is being formed and the area of calcified cartilage immediately in advance of the line of ossification both exhibit a dense impregnation with calcium salts in the form of much coarser granules, which are all contained within the matrix. An interesting point in this connection is that around each lacuna there seems to be a thin layer of matrix which might be interpreted as the capsule for the cartilage cell, and this capsule does not contain visible calcium salts. The clear wall which is thus formed around each space is quite noticeable.

If stages previous to the occurrence of the center of ossification are examined, the processes which terminate in the calcification of the cartilage may be followed from their beginning. The earliest appearance of a change in the normal cartilage consists of two elements, first an increase in the size of the cartilage cells, and second, a matrix which becomes pale and no longer stains well.

Marking the next stage the cartilage cells arrange themselves in groups, and between contiguous groups the amount of matrix is fairly heavy and forms a substantial, branching, trabecular network. This matrix is darker again, staining fairly deeply, and indicates the areas which in later stages become most heavily calcified. These are destined to be the supporting trabecular network of calcified cartilage which is not eroded during the process of ossification but which remains as a sort of scaffolding on which newly forming bone is deposited in the ossifying area.

PLATE I

Fig. 1.—Longitudinal section of the phalanges of the finger of a seven months human fetus, showing developing bone in the shaft; × 8.

Fig. 2.—Longitudinal section of the upper end of the humerus in a seven months human fetus. Note the numerous blood vessels in the cartilage forming the epiphysis, in which ossification does not commence until several months after birth; × 8.

Fig. 3.—Longitudinal section of the elbow joint of a seven months human fetus. Blood vessels are numerous in the cartilaginous ends of the bones, which do not ossify until years after birth; × 8.

All the illustrations are from photographs of specimens stained with hematoxylin and eosin except figure 10, in which the stain used was silver nitrate. The arrow, when used, points toward the center of the bone. In all the figures, *A.C.* indicates altered cartilage; *B.T.*, bone trabecula; *B.V.*, blood vessel; *C.C.*, cartilage cell; *C.C.T.*, calcified cartilage trabecula; *C.O.*, center of ossification; *G.D.*, granular deposit of calcium salts; *L.*, lacuna; *L.U.T.*, large, uncalcified trabecula; *L.W.*, lacunar wall free from granular deposit; *M.*, matrix; *P.*, periosteum; *P.M.C.*, primary marrow cavity; *S.T.*, stained trabecula and *U.C.*, unaltered cartilage.

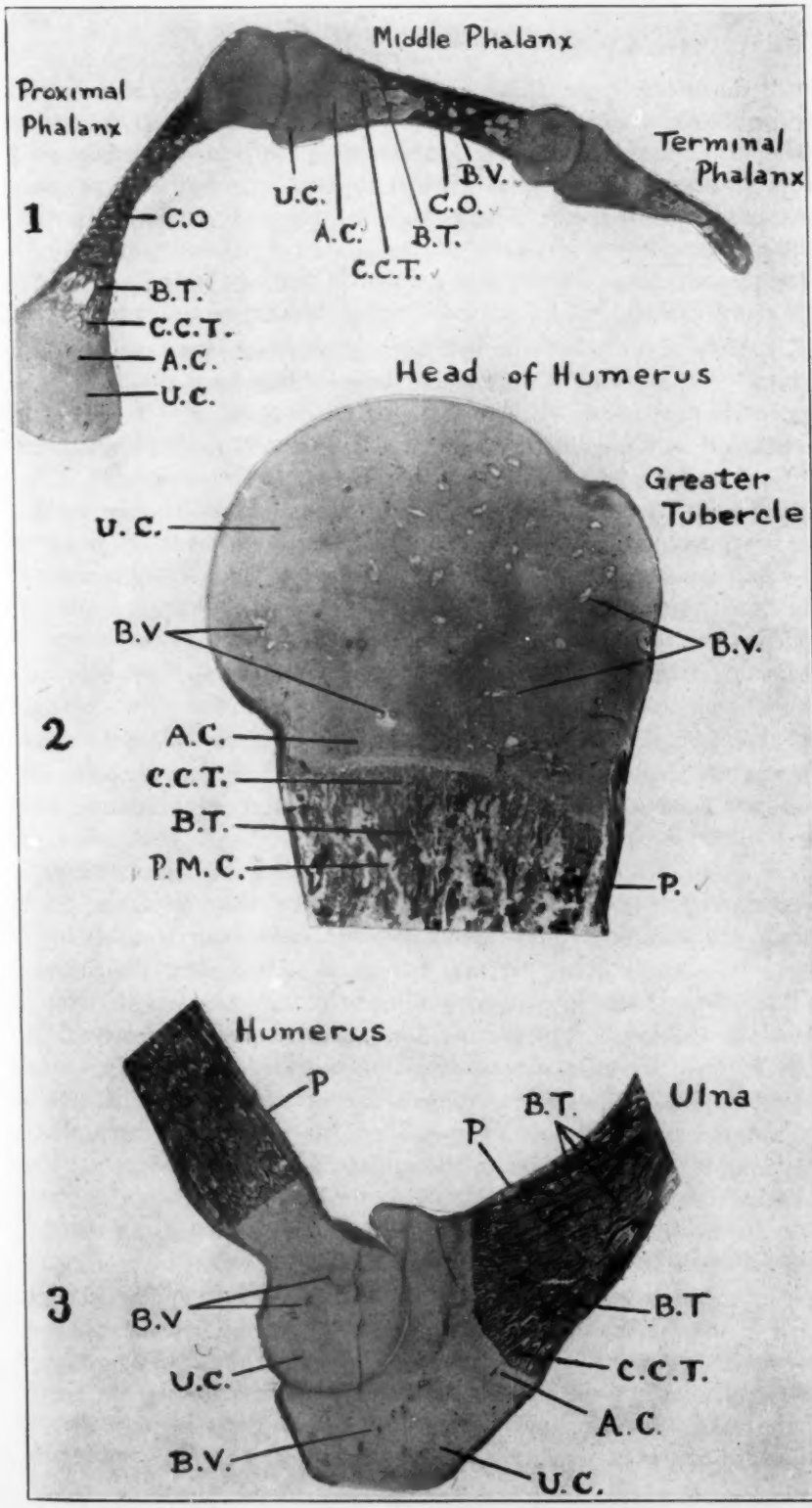
Middle Phalanx
Proximal Phalanx
Terminal Phalanx
1
C.O
U.C.
A.C.
C.C.T.
B.T.
B.V.
C.O.
B.T.
C.C.T.
A.C.
U.C.
Head of Humerus
Greater Tubercle
U. C.
B.V
B.V.
2
A.C.
C.C.T.
B.T.
P. M. C.
P.
Humerus
P
Ulna
B.T.
P
3
B.V
U.C.
B.V.
B.T
C.C.T.
A.C.
U.C.

PLATE I

Even before there is any visible deposit of calcium salts, the matrix of this trabecular network stains more deeply than the adjacent cartilage. The beginning of calcification in this region can be seen, and occurs as a deposition of small granules which appear first around the periphery of the lacunae of the cartilage cells. The thin layer of matrix forming the actual capsular wall of the lacunae is always clear of granules. The deposit increases and spreads in the matrix until the latter is completely filled with closely packed granules, which become almost a solid mass.

Calcification of Cartilage in Epiphyses of Long Bones.—The calcification of the cartilage of an epiphysis and its later ossification are initiated in the center of the mass. Before its appearance blood vessels are found in the epiphysis (figs. 2 and 3, plate I), invading it from various surfaces and branching within it so as to enclose a small central area within which are initated all the changes terminating in its conversion into bone. Included among the vessels are some which penetrate the epiphyseal plate and enter the epiphysis from the end of the shaft of the bone. In all respects the epiphysis develops as though it were an independent bone, and the process is exactly similar to that found in the short, irregular bones such as the tarsals and carpals next described, so that the epiphyses should evidently be included in this next class.

Calcification of Cartilage in Short, Irregular Bones.—In the epiphyses of the long bones and in such bones as the carpals and the tarsals, there are some interesting differences from the process of development seen in the shaft of the long bone. The navicular, cuboid, talus and calcaneus of older fetuses and new-born children provide particularly good specimens for examination, giving all stages from solid, unchanged cartilage to complete calcification and the formation of true bone.

In these cases it was learned that blood vessels enter the cartilage and ramify in it for long periods, sometimes for many months (fig. 4, plate II), before the changes begin which accomplish ossification. In spite of their presence, the cartilage remains unchanged. The vessels enter from all surfaces except those articulating with other elements of the skeleton and penetrate to a zone about midway to the center, where they branch and run parallel to the surface, anastomosing freely. This vascular zone thus surrounds a solid central core of cartilage, the surface of which in contact with the vessels will be the exact external surface of the future calcified center of the developing bone.

Some time before the center of ossification is due to appear, changes occur in the cartilage preparatory in character to this event. There is first noticed a marked augmentation in the size of the cartilage cells in the region of the vessels and just proximal to them toward the center of the mass. Accompanying this change is a great increase in the amount of matrix between cells, and this matrix stains poorly and is pale.

Immediately internal to the level of the blood vessels the cartilage cells now become irregularly grouped, not in columns as in the long bones but in clumps and small masses. Between these occur strips of matrix which do not contain cells, and which branch and intercommunicate and are destined to form the persisting cartilaginous network of trabeculae on which in later stages the first bone will be deposited. These trabecular areas give early indication of their future destiny (fig. 4, plate II; fig. 7, plate III, and fig. 10, plate IV) by staining more deeply than the remainder of the matrix and by being the first portion of the cartilage to become calcified. In later stages of development, it was quite noticeable that this intermediate trabecular zone adjacent to the blood vessels was completely calcified (figs. 5, 6 and 8), while the center of the mass still contained little if any calcium. Sections of a bone at this stage showed that there was a central region not yet calcified surrounded by a completely calcified layer; this again was surrounded by a ring of blood vessels and finally by a zone of unaltered cartilage on the exterior.

The first appearance of the deposition of calcium in these cartilages in every case was in the form of fine granules (fig. 11, plate IV) deeply stained with hematoxylin, lying in the matrix immediately outside the capsule of the cartilage cells, and always occurring first around those enlarged cells lying closest to the blood vessels. The primary zone of calcification is thus in the area of enlarged cartilage cells just internal or proximal to the blood vessels, and forms the calcified surface of a sphere (figs. 5 and 6, plate II), the center of which gradually calcifies later. This condition was extremely well shown in one talus which to the naked eye appeared completely calcified except for a thin external shell of unchanged cartilage, and which cut with some difficulty with the knife. In this specimen it was found, however, that cartilaginous trabeculae in the center of the area contained little if any calcium, although this was a later stage in calcification and the region was invaded by blood vessels and was full of primary marrow cavities, with beginning ossification of the area.

Blood vessels do not invade the central portion of the cartilage until it begins to calcify, but when once this process has taken place they erode and penetrate the periphery of the calcified mass (figs. 5 and 6, plate II) at various places and expand and anastomose within it, eroding large portions to form the primary marrow cavities. These are formed simultaneously with the occurrence of true ossification, which is now initiated with the deposition of bone by the osteoblasts on those calcified cartilaginous trabeculae which are not eroded. From this point onward, ossification advances toward the surface of the bone by growth on the

PLATE II

Fig. 4.—Horizontal section of a cuboid in a seven months human fetus. This bone ossifies in the ninth month but already there is a pale central area surrounded by one containing a network of darkly stained trabeculae lying just within the zone of blood vessels; × 8.

Figs. 5 and 6.—Sections of the talus (astragalus) of a seven months human fetus. The center of ossification occurs in this bone in the seventh month and is shown in the illustrations. It is really the center of calcification of the cartilage at this stage, and true ossification is just beginning to occur in it, coincident with its penetration by the blood vessels which are shown entering it; × 8.

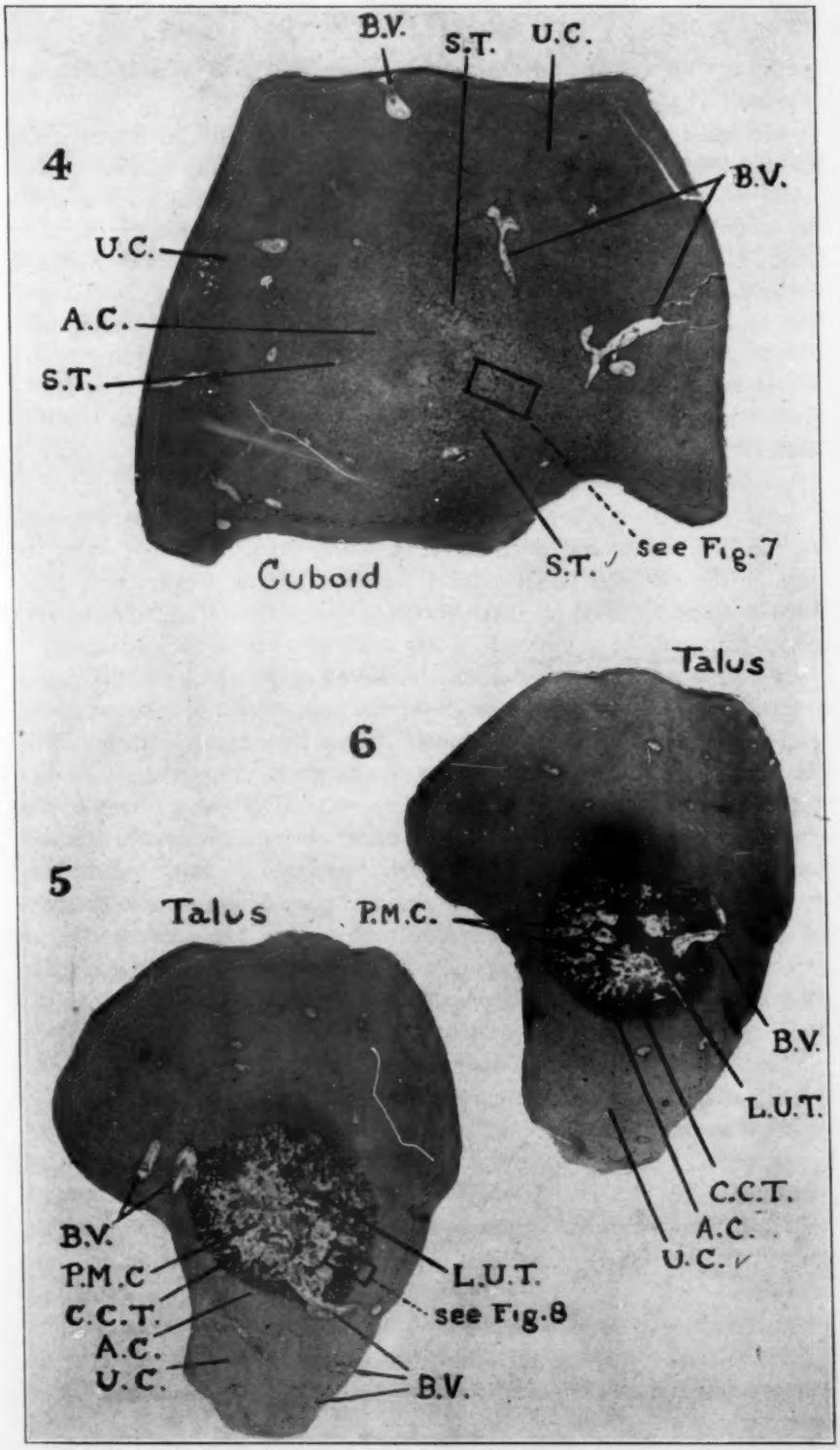
4
B.V.
S.T.
U.C.
B.V.
U.C.
A.C.
S.T.
S.T.
see Fig. 7
Cuboid
Talus
6
5
Talus
P.M.C.
B.V.
L.U.T.
C.C.T.
A.C.
U.C.
B.V.
P.M.C
C.C.T.
A.C.
U.C.
L.U.T.
see Fig. 8
B.V.

PLATE II

periphery of this central mass in the same way that it extends toward the ends of a long bone.

It will be seen that in all essential features calcification and ossification follow the same process in bones such as the tarsals as that followed in the long bones. The noticeable differences shown in the tarsal bones are: first, the early presence of blood vessels in the cartilage, long before the appearance of the centers of calcification and ossification; second, the appearance of calcium in the matrix at several places simultaneously to mark out a periphery for the region in which the alterations are occurring; third, the lateness of the occurrence of budding of the blood vessels and their formation of primary marrow cavities in the mass; fourth, the reversal of the direction of growth of the calcified area, which grows toward the entering blood vessels and not away from them as in the long bones.

Calcification of Cartilage in Bones of the Skull.—The development of the cartilage bones of the skull is similar in process to that in the rest of the skeleton and need not be described in detail. One point worthy of note, however, is the fact that calcification (fig. 9, plate III) may occur without any blood vessels being present in the cartilage.

In the skulls of young human embryos in which the cartilaginous rudiment of the future bones is not thick, it does not seem essential for their nutrition that blood vessels should be present in them. Preparatory to calcification, the matrix shows poor staining qualities and the cartilage cells enlarge as in other bones. The enlargement of the cartilage cells progresses until they are crowded one against another with a thin lattice or network of matrix between. At this stage, calcification of the matrix occurs by deposition of the calcium salts as granules in it. These granules are seen first immediately outside the circumference of the cells, and gradually those of contiguous cells merge to fill and make solid the partitions between adjacent cells. This obviously looks as though the placing of the granules was due to cellular activity.

Ossification follows this stage by the deposition of true bone subperiosteally on the calcified cartilage, and later this cartilaginous core to the future bone is gradually removed and replaced by true bone.

II. PHYSIOLOGIC CALCIFICATION DURING OSSIFICATION

Here two somewhat different conditions, due to the difference in origin of the bones developed in cartilage or in membrane, are considered.

Ossification of Membrane Bones.—In membrane bones the development was seen clearly in serial sections of the heads of young human embryos, the parietal bones and mandibles furnishing particularly good examples.

The matrix of the osseous tissue is of a fibrous nature. In the fibrous membrane which precedes those bones developed in this manner, there is a ground substance which is already prepared for impregnation with calcium salts in a permanent form. The deposition of calcium salts starts on the surface of the membrane while it is still thin. Here a layer of cells under the sheath and in relation to a fairly good blood supply begins to impregnate the fibrous tissue on which they lie with a fine granular deposit. This occurs first in contact with the periphery of that side of the cell in relation to the membrane. As the cell becomes embedded deeper and deeper in the new bone which is being formed, the granules are found extending farther around the cell until finally it is entirely enclosed in a calcified matrix and is now a bone corpuscle as distinguished from an osteoblast. In stained sections, the granules form a dark border outlining the cells.

It is almost universally believed that the bone forming cells here exude the fibrous organic matrix, and from my studies I believe that the calcium salts are also exuded into this matrix or simultaneously with the matrix, where they then crystallize out or precipitate to give the bone its strength and hardness.

Ossification of Bones Developed in Cartilage.—In bones developed in cartilage, there is no matrix ready for permanent impregnation with calcium. The cartilage lying in any zone about to be ossified becomes calcified, but much of this is immediately removed by erosion and absorption. What remains is merely a temporary scaffolding to support the true bone which is first laid down on it and covers it. When the quantity of bone becomes sufficient for its own support, even this part of the cartilage is finally removed.

The bone which is first formed is deposited as a thin layer on the surface of the trabeculae formed of calcified cartilage. It is deposited by the secretory activity of the osteoblasts, which exude the organic matrix and simultaneously seem to pass the calcium salts into it. These salts first become visible in the matrix in an extremely fine granular form, the granules being much more minute than those seen in calcified cartilage. Whether the calcium salts become solid by a process of crystallization out of the solution or a process of precipitation is not known. I believe that their presence in the matrix is, however, due to the secretory function of the osteoblast in placing them in this position.

NORMAL CALCIFICATIONS

In the previous part of the paper, the facts as gleaned from my investigations of the development of the skeleton have been presented. It remains now to review these and to state the conclusions to which one may be led by them.

PLATE III

Fig. 7.—Photomicrograph of the area outlined on cuboid in figure 4. The arrow points to the center of the bone. Note the darkly staining trabeculae, although a visible deposit of calcium salts cannot be identified; × 150.

Fig. 8.—Photomicrograph of the area outlined on talus in figure 5. The arrow points to the center of the bone. The cartilage cells are grouped in columns lying radially, and the dense black areas are the heavily calcified areas formed of closely packed granules. The granules are not visible in the photograph owing to the thickness of the section and the density of the stain taken by them; × 150.

Fig. 9.—Photomicrograph of a portion of the base of the cranium of a human embryo 43 mm. long. The heavy black areas between cartilage cells in the center of the section are calcified areas densely stained. Blood vessels are not present in this cartilage; × 150.

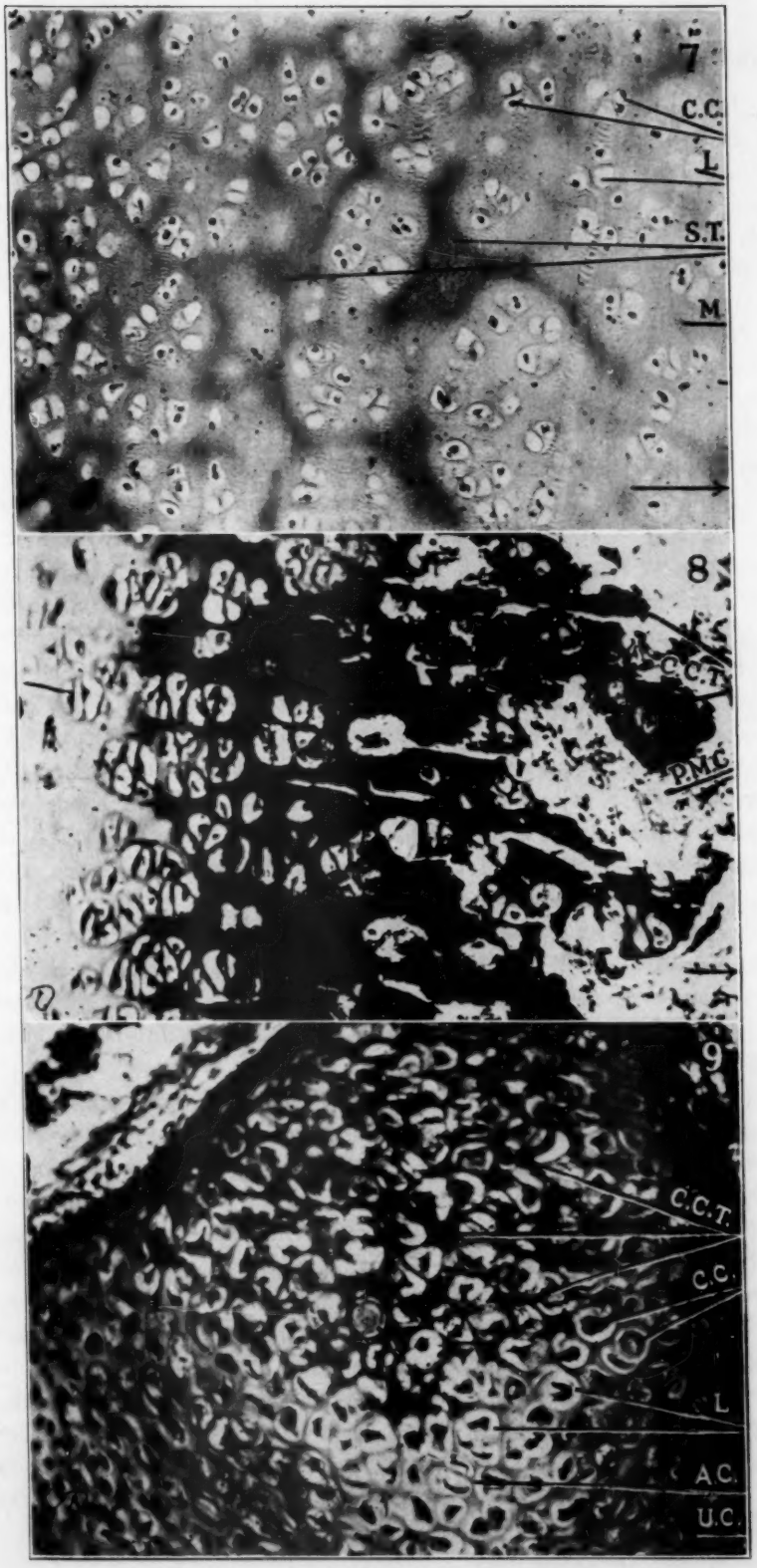

PLATE III

In the case of those bones which are preformed in cartilage, it may be stated that calcification of the cartilage occurs in all cases previous to ossification. The calcified cartilage is not transformed directly into bone but is removed. Much of it is immediately absorbed, while the remainder, forming a scaffolding of trabeculae for the support of the bone which is first produced, is later absorbed, when the true bone is formed in sufficient amount to support the skeleton.

The cartilage may go through all the changes ending in calcification, without the presence of any blood vessels (fig. 9, plate III) in it if it is small or thin, as may be seen in the case of some bones of the skull. But if the cartilage is of larger mass (fig. 2, plate I and fig. 4, plate II), then blood vessels will be present in it. However, they will stop just short of, and will not ramify in the calcified area itself until that moment (figs. 5 and 6, plate II) when the area is invaded by the budding blood vessels carrying in the osteoblasts to initiate true ossification.

An interesting view has been suggested to me to explain the presence of a skeleton formed of calcified cartilage in the embryo. It will be recalled that in the lowest forms among the vertebrates the skeleton is not true bone but is only a calcified cartilage. The bony skeleton first appears in the higher fishes, replacing a cartilaginous one. Thus the temporary appearance of a calcified cartilaginous skeleton for a short time just previous to the appearance of the permanent bony skeleton in the embryo of all higher vertebrates is to be interpreted as an evolutionary phenomenon, reflecting the past history of the race. It is a case of phylogeny being repeated in ontogeny in the skeleton in a way similar to that seen in the case of the kidney. In the latter, there is the succession of pronephros, mesonephros and metanephros as excretory organs, only the last persisting as a kidney in the highest vertebrates. In the skeleton one finds the succession of cartilage, then calcified cartilage and finally bone.

The calcifying of the cartilage, which is thus so temporary and transient, appears to serve a practical purpose in the embryo by providing a large amount of calcium ready for use by the osteoblasts in the first rapid formation of bone.

In those bones developed in membrane, the organic matrix necessary to receive the calcium salts is already present and does not need to be altered, as was the case with the cartilage, so the more permanent deposition of salts is made directly into this fibrous matrix. The latter is similar to the new matrix that is formed by the osteoblasts which produce bone in a cartilaginous area. The method of bone formation in membrane is therefore much like a calcification of fibrous tissue, with this difference, however, that the calcium salts appear in intimate relation with the characteristic tissue cells, namely, the osteoblasts and bone

corpuscles. The development of bone in membrane is, of course, also phylogenetically significant, for it, too, repeats the history of development of this type of bone.

In all cases of calcification of cartilage observed, the following facts are to be noted:

1. The calcium salts always appear first in the form of granules.

2. These granules appear first around the cartilage cell (fig. 11, plate IV) and are embedded in the matrix immediately outside of the cell capsule.

3. The salts appear before blood vessels are present in the calcified areas.

4. The calcium salts do not appear until after changes have occurred both in the cartilage cells (fig. 4, plate II; fig. 7, plate III, and fig. 10, plate IV) and in the matrix of the area to be calcified. The cells become grouped and greatly enlarged; the matrix increases considerably, becomes pale and stains poorly.

It thus appears that the association of calcium deposits with the cartilage cells is close and that the whole manner in which calcification occurs leads to the conclusion that the cell has considerable control of it, and that the calcium arrives in the matrix somehow as a result of the cell's activity.

According to all investigators, precipitation of calcium salts in solution in the body tissues occurs when the carbon dioxide content is lowered. It seems reasonable to infer that the matrix farthest away from the cells in the cartilage would contain the least carbon dioxide which, being a product of the activities of the cells, should be most concentrated in its immediate neighborhood. If this inference is correct, the first place in which calcium salts would be deposited would be in the larger masses of matrix and as remote as possible from surrounding cells. This is not the case, but the opposite is true. The first deposition is immediately surrounding the cell capsule, so that the granules evidently do not occur by precipitation from decrease of carbon dioxide in the cartilage.

The view has been put forth that calcium salts are precipitated as carbonate and phosphate by the reaction of these radicles excreted by the cells uniting with calcium dissolved in the fluids of the matrix. If this were so, one would expect the deposition to be equal all about the circumference of the cell, but in the early stages of calcification the deposit is frequently found lying all to one side of the cartilage cell, although there was plenty of opportunity for it to be surrounded completely.

PLATE IV

Fig. 10.—Photomicrograph of a section through a cuboid slightly further advanced than that shown in figures 4 and 7. The cartilage cells are in irregular groups with darkly staining heavy trabeculae between them, which will become calcified and form the scaffolding for the future deposit of bone; × 150.

Fig. 11.—Photomicrograph with high magnification of the area in a cuboid which is just beginning to calcify. The cells lie closely packed in irregular groups and in the matrix between them can be seen the black, densely stained masses of calcium deposit which in favorable places, when not too heavy, can be seen to be composed of closely packed granules. In those lacunae which are sharply in focus the actual lacunar wall is seen to be free from granules; × 500.

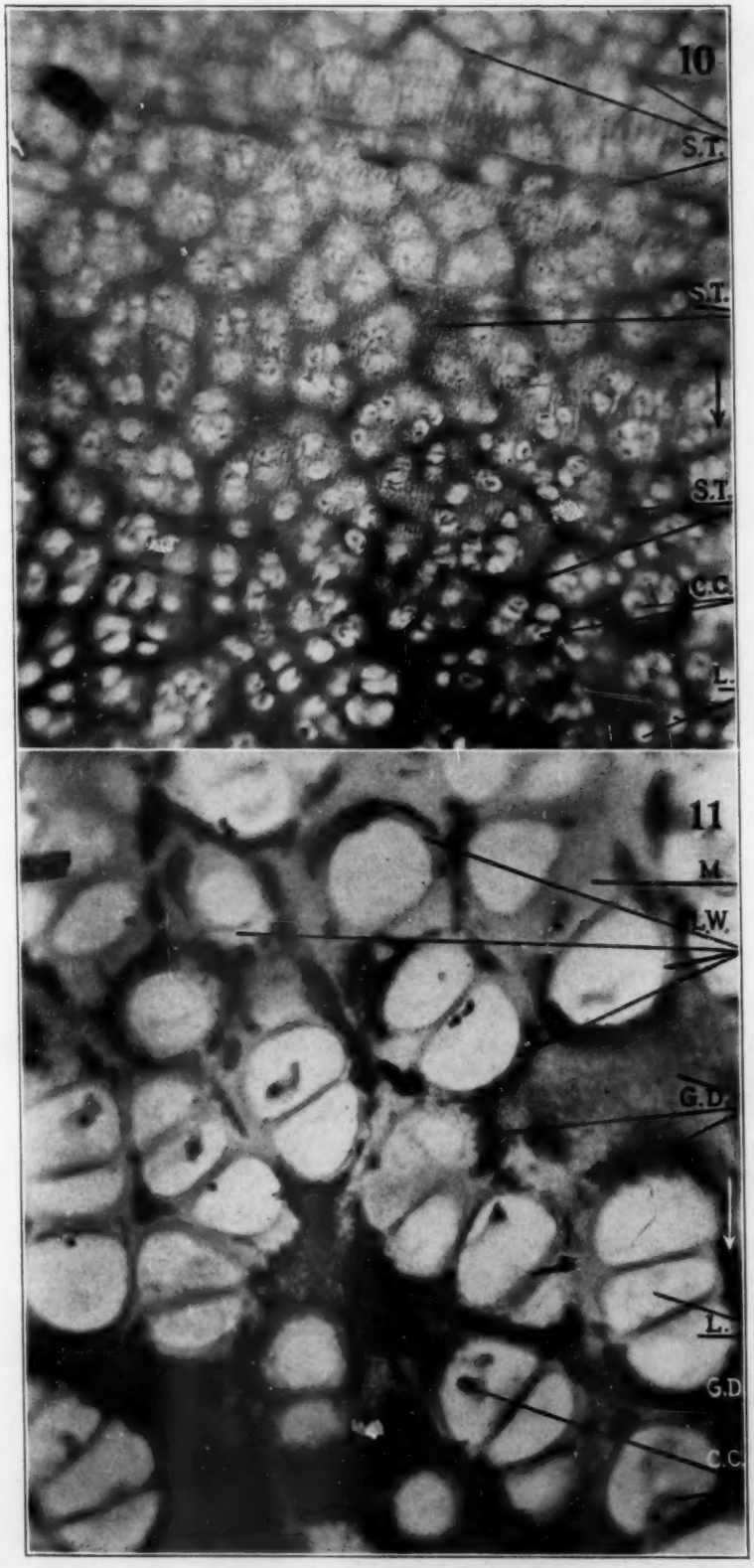

PLATE IV

It may be presumed that all the cartilage cells can excrete soluble phosphates and carbonates, yet calcium deposits do not surround all cells, but only those of one definite, particular zone.

If the cartilage cell secretes the calcium into the matrix, how does it accomplish it? Granules of the salts are not visible in the cell or its lacuna or passing through the capsule. The lacunae in cartilage are closed spaces, not a series of intercommunicating passages or canals through the cartilage, so one cannot look on them as open pathways conducting calcium salts in solution which might diffuse into the matrix and precipitate.

There are no blood vessels or lymph channels leading to individual cell lacunae in cartilage, and the common idea is that cartilage cells obtain all needed nutrient by imbibition of dissolved substances which diffuse through the matrix.

If, therefore, the cell obtains a supply of calcium it does so in dissolved form by diffusion through the same matrix in which the deposition is later made in solid form. This disposes of any view that the salts are excreted in liquid form and then precipitated in the matrix by lowering of carbon dioxide content, for the same matrix would have to possess a constitution which would allow calcium to pass in solution into the cells but not out again without being precipitated; this appears absurd. That there is calcium in the cartilage cells has also been demonstrated by Rabl.[2]

In studying the precipitation of calcium phosphate and carbonate in colloids in vitro, I noted a significant fact. With similar concentrations of reagents, it was more difficult to produce precipitation of the calcium salts in aqueous extracts of cartilage than in any other medium employed. There was always a much smaller quantity of precipitate obtained in these cases. This forms a strong argument against the view that cartilage calcifies by a simple precipitation reaction. Bechhold[3] also noted that cartilage shows a selective adsorption of calcium.

From experiments on puppies, Jones[4] concluded that two factors influence calcification. The more important one is the metabolic state inherent in the animal, and the other is diet, which influences the metabolism of the cells. The balance of ions between the bone-forming cells and their surroundings determines the deposition of bone salts. Any agent changing the metabolism of the bone cells will alter this ionic balance and will influence the deposition or the absorption of bone.

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2. Rabl, R. H.: Ueber die Kalkablagerung bei der Knochenentwicklung, Klin. Wchnschr. **2**:1644, 1923.

3. Bechhold, H.: Colloids in Biology and Medicine, translated by J. G. M. Bullowa, New York, D. Van Nostrand Co., 1919.

4. Jones, Martha R.: Studies on Inorganic Salt Metabolism: III. On Certain Factors Which Influence the Deposition and Resorption of Bone, Am. J. Physiol. **79**:694, 1926-1927.

A definite proportion was shown by Wells [5] to exist between the amount of calcium carbonate and phosphate in bone and calcified cartilage. In normal persons, there are fifteen parts of calcium carbonate to eighty-five parts of calcium phosphate, or in the chemical proportions of one molecule of the carbonate to three of the phosphate.

The salts present in bone have been recently analyzed by Howland, Marriott and Kramer.[6] They concluded that calcium is present only in the form of neutral calcium carbonate and tricalcium phosphate. The ratio of phosphate to carbonate depends directly on the amount of phosphates in the blood serum and is therefore lower in rickets, in which the phosphorus content is markedly reduced, than it is in health. In artificial mediums the ratio of phosphate to carbonate in the precipitate is in direct proportion to the quantities dissolved in the mediums, and can be obtained in the same relative amounts as in bone. However, the authors stated that the latter fact must not be taken to indicate that calcification is a process of simple precipitation, as they have shown that other factors have to be taken into account.

Shipley, Kramer and Howland [7] took slices of cartilage from developing bones and immersed them in solutions containing calcium salts, where they were then incubated. Calcification of the cartilage occurred in nine hours with normal blood concentrations of calcium and phosphorus and at the normal hydrogen ion concentration of serum. This calcification was always in the matrix, never in the cells, and was not on the surface of a slice, but always in the depths of its thickness. Microscopic examination did not show any differences from the calcification of cartilage seen during normal development of bone.

Costochondral junctions in children dying of rickets did not calcify in rachitic serum, but the process did occur when they were immersed in normal serum.

Calcification did not occur after the cartilage was boiled or after the use of antiseptics or protoplasmic poisons. This clearly indicates the active part which the cell must play in the process.

With the addition of 1 per cent of egg albumin to the solutions, calcification did not occur in forty-eight hours, but if the slices of cartilage were washed at the end of twenty-eight hours and placed in fresh solutions without albumin calcification took place. This indicates that calcium when bound to a protein is not easily utilized by the cell,

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5. Wells, H. G.: Pathological Calcification, J. M. Research **9**:491, 1906; Calcification and Ossification, Harvey Lectures, 1910-1911; Calcification and Ossification, Arch. Int. Med. **7**:721 (June) 1911; Chemical Pathology, ed 3, Philadelphia, W. B. Saunders Company, 1918.

6. Howland, John W.; Marriott, McKim and Kramer, B.: Studies Upon the Inorganic Composition of Bone, J. Biol. Chem. **68**:721, 1926.

7. Shipley, P. G.; Kramer, B., and Howland, J.: Studies upon Calcification in Vitro, Biochem. J. **20**:379, 1926.

and that it is the ionized calcium in the blood serum which is readily available for calcification.

That part of the calcium in the blood serum is not ionized and is bound to some protein was demonstrated by Marrack and Thacker,[8] who also showed that a change of hydrogen ion concentration of from 7.4 to 7.8 reduces the calcium ion concentration 60 per cent. In regard to the latter point the work of Jones is significant, as she showed that destruction of bone in rickets is much greater as the alkalinity of the tissues is increased by appropriate diets and healing tends to occur with the administration of acids.

A nondiffusible, nonionizable portion of the calcium in the blood, bound to a protein component, was also shown by Updegraff, Greenberg and Clark,[9] and by Hastings, Murray and Sendroy.[10]

Freudenberg and György [11] expressed the belief that in some way calcium is bound to the protein constituent of the cartilaginous matrix and reacts with phosphates and carbonates to form the hard deposit evident in calcification. Products of tissue degeneration as well as urea and ammonium salts prevent calcification. The phosphate and carbonate formed may secondarily split off as inorganic salts from the protein and leave the latter free to repeat the process, thus increasing the calcification.

According to Bergeim, rachitic rats lose both calcium and phosphorus in the feces, while normal animals absorb these elements. Therefore, rickets is not only a pathologic condition of the bone but shows derangement of other parts of the body. Telfer [12] demonstrated similar conditions in human beings and showed that administration of cod liver oil caused great increase in absorption of both calcium and phosphorus.

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8. Marrack, J., and Thacker, G.: The State of Calcium in Body Fluids, Biochem. J. **20**:580, 1926.

9. Updegraff, H.; Greenberg, D. M., and Clark, G. W.: A Study of the Distribution of the Diffusible and Nondiffusible Calcium in the Blood Sera of Normal Animals, J. Biol. Chem. **71**:87, 1926.

10. Hastings, A. B.; Murray, C. D., and Sendroy, J., Jr.: Studies of the Solubility of Calcium Salts: I. The Solubility of Calcium Carbonate in Salt Solutions and Biological Fluids, J. Biol. Chem. **71**:723, 1926. Sendroy, J., Jr., and Hastings, A. B.: II. Solubility of Tertiary Calcium Phosphate in Salt Solutions and Biological Fluids. III. Solubility of Calcium Carbonate and Tertiary Calcium Phosphate Under Various Conditions, J. Biol. Chem. **7**:783, 1926.

11. Freudenberg, E., and György, P.: Kalkbindung durch tierische Gewebe, I to X Biochem. Ztschr. **110**:299, 1920; **115**:96, 1921; **118**:50, 1921; **121**:131, 1921; **121**:142, 1921; **124**:299, 1921; **129**:134, 1922; **129**:138, 1922; **142**:407, 1923; **147**:191, 1924.

12. Telfer, S. V.: Studies in Calcium and Phosphorus Metabolism: IV. The Influence of Free Fatty Acids in the Intestine on the Absorption and Excretion of the Mineral Elements. V. Infantile Rickets. The Excretion and Absorption of the Mineral Elements and the Influence of Fat in the Diet on Mineral Metabolism, Quart. J. Med. **20**:1, 1926.

His conclusion is that faulty utilization of bone forming elements in rickets is due to defective absorption and that this in turn depends on a change in gastro-intestinal conditions.

Wilkins and Kramer [13] proved that the beneficial effect of cod liver oil on rickets could be obtained by an ether soluble extract injected intramuscularly, showing that the effect is a general one exerted through the circulation and not a local one simply due to the presence of the oil in the intestine. Flamini [14] showed that the antirachitic vitamin in cod liver oil increases the absorption of calcium from the intestine and aids in its fixation in the tissues.

In spite of their lower concentration in the blood of rachitic individuals the calcium salts are present in a supersaturated solution, according to Holt, La Mer and Chown,[15] and so the failure of the salts to be deposited in the bones must be due to more than a simple lack of precipitation.

Beckhold stated that precipitation of calcium is hindered by the colloids in the blood, and this hindrance must be prevented during ossification, the protective action of the colloids being changed at or by the bone cells. He also noted that Witte's peptone holds only calcium carbonate in solution, while calcium phosphate precipitates out of it. In this he saw the explanation of why there is so much more phosphate than carbonate in bone, because peptones are formed as the cartilage breaks down ahead of the ossification. In rickets there is an overgrowth of cartilage with less breaking down and, consequently, a smaller deposition of calcium salts and a softer bone.

Further evidence of the part played by the cell in the deposition of calcium in bone and cartilage is seen in the work of Robison, Kay, Soames and others.[16] They demonstrated that those tissues which utilize phosphates all possess a ferment called phosphatase, or esterase,

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13. Wilkins, L., and Kramer, B.: Infantile Rickets: Treatment by Intramuscular Injection of a Cod Liver Oil Concentrate, Bull. Johns Hopkins Hosp. **40**:52, 1927.

14. Flamini, Mario: The Action of the Antirachitic Vitamin of Cod Liver Oil on the Organism of the Child, Pediatria **34**:625, 1926 (Child Devel. Abstr.).

15. Holt, L. E.; La Mer, V. K., and Chown, H. B.: Studies in Calcification: I, II and III, J. Biol. Chem. **64**:509, 1925.

16. Robison, R.: The Possible Significance of Hexosephosphoric Esters in Ossification: I., Biochem. J. **17**:286, 1923. Robison, R., and Soames, K. M.: The Phosphoric Esterase of Ossifying Cartilage, Biochem. J. **18**:740, 1924. Kay, H. D., and Robison, R.: The Action of the Bone Enzyme on the Organic Phosphorus Compounds in Blood, Biochem. J. **18**:755, 1924. Goodwin, H. W., and Robison, R.: Phosphoric Esters of the Blood, Biochem. J. **18**:1161, 1924. Martland, M., and Robison, R.: The Enzyme in the Early Stages of Bone Development, Biochem. J. **18**:1354, 1924. Robison, R., and Soames, K. M: A Chemical Study of Defective Ossification in Rachitic Animals, Biochem. J. **19**:153, 1925. Kay, H. D.: Kidney Phosphatase, Biochem. J. **20**:791, 1926; The Function of a Phosphatase in Bone Formation, Brit. J. Exper. Path. **7**:177, 1926.

which will produce inorganic, ionizable phosphates from organic phosphoric esters. The phosphatase varies with the animal, the tissue and the age; it will stand considerable heat and can be kept for months and will still remain active.

Kidney phosphatase will hydrolyze all the acid-soluble phosphates in the blood, while bone phosphatase will hydrolyze only part of them. Bone phosphatase is not present before the beginning of ossification or in the cartilaginous ends; it is present in quantity in all bone, even in old age and is in maximum amount in the ossifying zones during growth and is coincident with and in proportion to the amount and rapidity of growth.

Eden [17] found large amounts of calcium in the callus of healing fractures, which were transparent on roentgenographic examination. The calcium was evident here in a form bound to the protein of the callus. He also made injections of solutions of calcium salts into the site of fracture and obtained much more rapid healing, showing the effect of a good supply of calcium on cellular activity.

Rabl [2] said that the calcium in growing bones is to be found in a form bound to peptids and amino-acids formed by the breaking down of the cartilage in the region. Carbonates are produced through the liberation of carbon dioxide on further decomposition and the phosphates precipitate by reaction with soluble phosphates of the tissue fluids. One might see here the use of the esterase previously mentioned in increasing the amount of available phosphates.

The problem raised here does not yet appear capable of solution, but consideration of the facts leads to the assumption that the cell must have considerable influence on the deposition of calcium salts in cartilage. The weight of evidence, one feels, is in favor of the view that the cartilage cell has some secretory activity, the exact process of which is as yet unknown, which is accountable for placing the calcium in the matrix.

This view is similar to the one I have already advanced that the calcium contained in the matrix of the bone is deposited by secretory activity of the osteoblasts and bone corpuscles, and my reasons for inclining to this view have been fully set forth in previous papers.[18]

The deposition of calcium in bones developed in membrane, being in the form of fine granules immediately surrounding the osteoblasts

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17. Eden, R.: Untersuchungen über Vorgänge bei der Verknöcherung, Klin. Wchnschr. **2**:1798, 1923.

18. Watt, J. C.: The Behaviour of Calcium Phosphate and Calcium Carbonate (Bone Salts) Precipitated in Various Media, with Applications to Bone Formation, Biol. Bull. **44**:280 (June) 1923; The Deposition of Calcium Phosphate and Calcium Carbonate in Bone and in Areas of Calcification, Arch. Surg. **10**:983 (May) 1925; The Transport and Deposition of Calcium Salts in the Body, M. J. Australia **2**:85 (July) 1925.

(which also form the bone corpuscles when fully embedded), is in all essentials similar to the process of calcification of cartilage, and its consideration leads to similar conclusions.

It is interesting to note in this regard that Weidenreich [19] published two comprehensive articles on the constitution of bone, in which he described three divisions of this tissue: fiber bone, cartilage bone and lamellar bone. He considered the lamellar bone of the haversian systems as being the only true organized bone tissue, with true bone corpuscles and with a finely granular calcium content to its matrix, which may be even homogeneous from fusion of the deposits into a mass.

Fiber bone is regarded as simply a dense calcification of fibrous tissue; it is found as the subperiosteal deposit on the surface of all bones, in muscular prominences of the skeleton and in all the bones formed in membrane. It can also be seen in ossified tendons. The deposit of calcium here is in a much coarser granular form.

Cartilage bone is seen in the early embryonic ossifications and also in the calcification of certain epiphyses, especially those occurring late, and contains calcium in a coarse granular form.

The two latter forms of bone appear in the embryo and also during later growth as the kind of bone which is formed first in any location. Much of this material is later reorganized and converted into the lamellar type by activity within the bone. What I have found true, especially concerning the physical state of the calcium salts in various bones, is in perfect accord with Weidenreich's statement.

Two other instances of normal calcification which may be considered are the formation of the shell in the hen's egg and the shell of the fresh water clam. Both of these structures are regarded as products of secretion. The clam shell is considered due to the secretion of calcium carbonate in albumin on the surface of the animal's mantle. This salt, as Pauli and Samec [20] showed, is seven times as soluble in albumin as in water and so can be secreted in appreciable quantity. The solubility is also increased by the carbon dioxide content of the tissues. When the secretion is exuded on the surface of the mantle, the lowered carbon dioxide content of the water causes the calcium carbonate to precipitate. Being in a colloidal solution it separates out in the colloidal form of deposit, which is usually small spherules; these have a marked

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19. Weidenreich, F.: Knochenstudien: I. Ueber Aufbau und Entwicklung des Knochens und den Character des Knochengewebes. II. Ueber Sehnenverknocherungen und Factoren der Knochenbildung, Ztschr. f. Anat. u. Entwicklungsgeschichte, **69**:382 and 558, 1923; Ueber den Begriff "Knochen" und die Beziehungen des Knochengewebes zu Bindegewebe und Knorpel, Anat. Anz. **57**:138, 1923.

20. Pauli, W., and Samec, M.: Ueber Löslichkeitsbeeinflussung von Electrolyten durch Eiweisskörper, Biochem. Ztschr. **17**:235, 1909.

tendency to fuse and so produce the dense pearl shell. The contact of the water with the albuminous solution no doubt aids in the precipitation also by its tendency to dilute the albumin and so render the contained calcium salt less soluble.

The process of formation of the clam shell is thus seen to be a double process. There first occurs secretion of the calcium carbonate in a soluble form in an albuminous matrix through the agency of the mantle cells. Secondly, there is a precipitation and fixation of this secretion by physical and chemical means, through which the calcium carbonate combined with the albumin in colloidal crystals is deposited. That albumin combines with the crystals was shown previously as far back as Rainey's [21] period by decalcifying experimental precipitates and obtaining perfect albuminous casts of the deposits after the calcium is removed.

A second example of the secretion of calcium is to be found in the formation of the shell of a bird's egg. The shell is composed almost entirely of calcium salts and is secreted by the shell gland, a modified part of the genital tract, and an evident and undeniable cellular activity is concerned here in the output of calcium. The final deposition in solid form about the egg may again be a precipitation due to the concentration of carbon dioxide found in the genital passage which is lower than the concentration existing in the tissues. But the placing of the calcium here where it can precipitate is certainly due to the secretory work of the mucosa of the shell gland in taking the calcium salts from the blood stream and passing them through to its free surface.

In the case of the formation of the teeth, the manner in which calcium is deposited again comes into question. There is a definite organic matrix to both the enamel and the dentine, laid down, respectively, by the ameloblasts and the odontoblasts.

In the matrix of each layer, the calcium is found deposited in the form of minute granules. These were interpreted by Rainey, and by others since his time, as indicating their production by precipitation, as they are exactly of the form and appearance seen in experimental precipitation of calcium carbonate in colloids. But the inorganic material of the teeth is largely calcium phosphate, which has been shown (Rainey,

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21. Rainey, G.: On the Formation of the Skeletons of Animals, and Other Hard Structures Formed in Connection with Living Tissues, Brit. & Foreign Med. Chir. Rev. **40**:343, 1857; Precise Directions for Making of Artificial Calculi with Some Observations on Molecular Coalescence, Quart. J. Micr. Sc. **6**:41, 1858; On the Structure and Mode of Formation of the Dental Tissues, According to the Principle of Molecular Coalescence, Quart. J. Micr. Sc. **7**:212, 1859; Some Further Experiments and Observations on the Mode of Formation and Coalescence of Carbonate of Lime Globules, and the Development of Shell Tissues, Quart. J. Micr. Sc. **1**:23, 1861.

Harting,[22] Watt) to precipitate even in colloids as an extremely fine granular suspension. Only the carbonate forms globules and spherules, so that the constant appearance of the calcium phosphate in the teeth in globular form is not to be interpreted without question as indicating a simple precipitation.

The problem as to how the calcium actually deposits in the enamel or the dentine of a tooth is underlaid by a still more fundamental problem as to how the calcium salts are brought into this region where they are later laid down. If they simply diffuse into the matrix, then the whole process of deposition is a simple precipitation. But if they are selected and passed into the region by cellular activity and then appear as a solid deposit, it is evident that although the end of the process may still be a precipitation, nevertheless, the beginning is a vital process, secretion by the cells forming this tissue. This is an important and far reaching difference and is of great significance in understanding the development of the teeth; it will modify ra ally all attempts to treat abnormal conditions such as defective cal tion.

Concerning the teeth, Blotevogel [23] did work which is of great significance. He made injections of trypan blue into young mice and then examined the developing teeth at intervals of from one to thirty days. He found that the ameloblasts, which form the enamel, and the odontoblasts, which produce the dentine, both stored the vital dye evenly throughout the cell before they became active. But when they began to form the enamel and dentine, both these types of cells showed marked polarity, with a definite direction of transport of material through the cell. This was shown by the fact that all granules became closely packed along that edge of the cell which was forming the enamel or the dentine. The organic matrix of the enamel or dentine formed during the period when the dye was present was also colored diffusely blue.

When the enamel and dentine became calcified the parts which contained calcium were colorless, either because the calcium does not combine with the dye or because it bleaches it. This is the opposite effect to that seen with madder or alizarin, which combines with calcium, as shown by Macklin,[24] and is deposited with it as a colored compound if the dye is present at the time of deposition.

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22. Harting: On the Artificial Production of Some of the Principal Organic Calcareous Formations, Quart. J. Micr. Sc. **12**:118, 1872.

23. Blotevogel, Wilhelm: Beiträge zur Kenntnis der Stoffwanderungen bei wachsenden Organismen: II. Der vitale Farbstofftransport während der Zahnentwicklung, Ztschr. f. Zellen-u. Gewebelehre **1**:601, 1924.

24. Macklin, C. C.: Studies in Calcification by the Use of Vital Dyes, J. M. Research **31**:493, 1917.

Blotevogel found conditions in bone similar to those in dentine, uncalcified matrix colored with trypan blue and calcified areas unstained. The osteoblasts, forming matrix on all sides of them, stored the blue evenly in contrast to the odontoblasts which, forming dentine only on one side, stored all the blue at that side. A definite direction of transport of material and an evident cellular activity in handling this material has been beautifully demonstrated here. It may be inferred that what can be done in the case of trypan blue could be done also in the transport of calcium salts. A definite cellular activity can be demonstrated in the formation of the organic matrix of tooth, bone and cartilage, and the evidence all seems to point to the occurrence of a similar process in the impregnation of this matrix with the calcium salts.

Further collateral evidences that cellular activity is responsible for the handling of calcium in bone and cartilage may be cited. In Vincent's [25] book on "Internal Secretions and the Ductless Glands" are many instances, given with reference to original papers, of the influence of hormones on the growth of bone. The changes in acromegaly, the increased stature in eunuchs, the increased growth of bone in cretins treated with thyroid extract and other instances all go to show the effects of hormones.

Hammet [26] showed that thyroid and parathyroid deficiencies produce marked changes in the bones, especially in proportions of water, organic matter and bone salts. Parathyroidectomy lowers the calcium and phosphorus content and increases the amount of magnesium. This author also showed that all bones are not equally sensitive to disturbances in hormone control, the humerus, for example, being less resistant than the femur.

Rachitic changes in the bones of rabbits and rats the thyroid glands of which were removed three weeks after birth were demonstrated by Kunde and Williams [27] in spite of the administration of adequate diets to the animals.

Fahr [28] described marked changes of the endocrine system in the case of osteogenesis imperfecta and expressed the belief that these

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25. Vincent, S.: Internal Secretions and the Ductless Glands, Toronto, The McMillan Company, 1912.

26. Hammet, F. S.: Studies of the Thyroid Apparatus: XLII. The Rôle of the Thyroid and Parathyroid Glands in the Growth of the Long Bones, J. Exper. Zool. **47**:95, 1927; XLIII. The Rôle of the Thyroid and Parathyroid Glands in the Growth of the Long Bones, ibid. **47**:95, 1927; XLIV. The Rôle of the Thyroid and Parathyroid Glands in the Chemical Differentiation of Bone During Growth (Ash, Organic Matter and Water), J. Biol. Chem. **72**:505, 1927.

27. Kunde, M. M., and Williams, L.: Studies on Experimental Cretinism: II. Nutritional Disturbances of Bones, Proc. Soc. Exper. & Med. **23**:814, 1926.

28. Fahr, T.: Endocrine System in Osteogenesis Imperfecta, Virchows Arch. f. path. Anat. **261**:732, 1926 (Child Devel. Abstr.).

changes are the fundamental factor causing dysfunction of the osteoblasts. By means of x-ray examinations on the living, Engelbach and McMahon [29] also showed marked changes in bone in various endocrine disorders. It is the general belief that hormones act on the cells of a tissue, which is much more probable, especially in the case of bone, than any hypothesis as to a chemical action on the matrix and its calcium content.

In a similar way vitamins are supposed to act on the cell, and McCarrison [30] showed marked changes in bone in cases of vitamin deficiency. In addition, Miles and Feng [31] studied many cases of osteomalacia in China and came to the conclusion that it is a deficiency disease due to lack of fat-soluble vitamins. They noted that there might be a calcium deficiency in the diet and in the blood at the same time, but this was not always so. Without a deficiency of calcium in the body, such a condition as osteomalacia can be conceived of only as a disease in which the bone cell is at fault. It was also noted that administration of cod liver oil caused bone growth for more than two months after the cessation of treatment.

The normal growth of bone and the deposition of a proper calcium content in its matrix is stimulated by sunlight and by ultraviolet light in cases of rickets. This surely must occur by action on the tissue cells of the bone. In a review of the causes of rickets, Tisdall [32] pointed out that a deficiency in the calcium content of the body is not sufficient in itself to cause this disease, whether the calcium is deficient either from diminished intake or from increased loss. A deficiency of vitamins alone or of phosphates alone will not produce rickets, but this deficiency leads only to osteoporosis by a failure to produce as large and heavy an amount of bone as necessary. Either a deficiency of calcium or a deficiency of phosphates combined with a deficiency in vitamins does, however, produce typical rickets. Robison and Soames [33] obtained similar results in experiments on rats. As every change in the various conditions already cited, except the deposition of the calcium in the bony matrix, is admittedly due to the activity of the bone cells, it seems reasonable to suppose that the deposition of calcium might also be ascribed to the cell's activities, as it occurs in such close correlation with

29. Engelbach, William; and McMahon, A.: Osseous Development in Endocrine Disorders, Endocrinology **8**:109 (Jan.) 1924.

30. McCarrison, R.: Studies in Deficiency Disease, London, Henry Frowde and Hodder and Stoughton, 1921.

31. Miles, L. M., and Feng, C.: Calcium and Phosphorus Metabolism in Osteomalacia, J. Exper. Med. **41**:137, 1925.

32. Tisdall, F. F.: The Etiology of Rickets, Canad. M. A. J. **11**:934 (Dec.) 1921.

33. Robison and Soames (footnote 15, fifth reference).

all the other activities. Medes [34] showed that the bones of rats on a diet poor in phosphorus exhibit rachitic changes, while diets low in calcium content lead only to osteoporosis.

It is to be particularly noted that cells having to do with the special use of calcium for structural purposes are not all of one kind. Three types of epithelium are found capable of secreting calcium to form solid structures: namely, the epithelium of the mantle of the clam, the epithelium of the shell gland of the bird, and that of the enamel organ of the tooth. Three types of connective tissue cells are similarly concerned: the cartilage cell, the osteoblasts and bone corpuscles and, finally, the odontoblasts of the teeth.

The view is readily accepted that the shell of the clam and the shell of the bird's egg are products of secretion, both the organic matrix and the calcium salts being present through the secretory function of the cells. It is generally admitted also that the organic matrix of bone and cartilage and of the enamel and dentine of the tooth are products of the cell. In the latter cases, why should not calcium also be present because of the secretory activity of the cells?

SUMMARY

Development of Bone.—1. Intramembranous bone develops by the simple calcification of a fibrous matrix, osteoblasts gradually walling themselves in with a finely granular deposit.

2. The formation of endochondral bone shows a progressive series of marked changes. The cells in the cartilage that are about to change enlarge, and the matrix increases in quantity and stains poorly. The cartilage cells then become segregated into groups between which lie the main, heavy trabeculae, and the matrix again stains deeply and calcifies by deposition of granules.

Blood vessels bearing osteoblasts now invade the calcified cartilage, eroding the narrower trabeculae and occupying the lacunae, from which the cartilage cells have disappeared. Osteoblasts deposit true bone on the remaining trabeculae; this first bone and the calcified trabeculae on which it lies are later reorganized, and an arrangement better suited to the structure as a whole is laid down.

A calcified cartilage skeleton, temporary in duration and replaced by bone, is an evolutionary phenomenon and repeats in the individual the history of the race.

Endochondral bones of different shapes and sizes show individual modifications in their process of development.

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34. Medes, G.: Rats on Diets High in Phosphorus and Low in Calcium, Proc. Soc. Exper. Biol. & Med. **23**:679, 1926.

(*a*) Long bones are invaded at the center of the shaft by blood vessels which bud and grow rapidly and carry in osteoblasts with them. Calcified cartilage always lies just ahead of the vessels and is continually invaded and its line pushed back until the whole shaft is ossified. The calcified cartilage grows away from the entering vessels. Blood vessels are not present in the shaft before the process of ossification begins.

(*b*) Epiphyses and short irregular bones such as the carpals and tarsals contain blood vessels long before ossification begins. These vessels extend about half way to the center and then branch and anastomose. The central area bounded by them calcifies and is then invaded by budding vessels carrying in osteoblasts. The cartilage is eroded except for some larger trabeculae; the zone is ossified and then extends its boundaries until it reaches the periphery of the bone. In this case the calcified cartilage extends toward the entering blood vessels, not away from them as seen in the shafts of long bones.

(*c*) Endochondral bones of the skull may show enlargement of the cartilage cells and calcification of the matrix without the presence of any blood vessels until the moment when they are penetrated by budding vessels accompanied by osteoblasts.

Form of Calcium Deposits.—1. In Cartilage: The deposit is always in the form of distinct granules which accumulate in closely packed masses but do not fuse. The granules appear first in the matrix immediately around the cartilage cells, but there appears to be a thin envelop or capsule forming the actual wall of each lacuna which is free from granules. The granules appear first around those cells nearest to blood vessels.

2. In Bone: The deposit is always granular. The granules are minute, much smaller than those in cartilage, and they may fuse to form a homogeneous mass. The granules appear first in the matrix in immediate contact with the osteoblasts.

Manner of Deposition of Calcium Salts.—In normal calcification of cartilage and bone, the deposition of the calcium salts is presumed to be due to cellular activity, because the first evidence of deposition is always immediately about the cell and can occur only after definite changes in the cell and in the organic matrix formed by it (Watt). It has also been shown that precipitation of calcium salts is difficult in a cartilage extract (Watt [18]), and solutions of calcium phosphate in conditions similar to those in the tissues can exist for a long period without precipitating (Holt, LaMer and Chown [15]) and normal blood is 200 per cent saturated.

Slices of normal living cartilage will calcify rapidly when incubated in proper solutions, but will not do so if the cells are killed (Shipley, Kramer and Howland [7]). Cells forming the enamel and dentine of the

teeth show a definite storage and direction of transport of trypan blue, and bone cells show similar activities (Blotevogel [23]).

Secretions of the ductless glands exert a marked influence on growth of bone, and cell tonics such as sunlight, ultraviolet light and vitamins also show marked effects. Bone and calcifying cartilage are shown to possess a ferment, esterase, which will convert organic phosphates into inorganic compounds (Kay and Robison [16]).

Collateral evidence of the power of cells to secrete calcium salts to form hard structures is shown by the epithelium of the mantle of the clam in producing the clam shell and the epithelium of the shell gland in producing the shell of the bird's egg.

Bones become rarefied when blood calcium is low, as in pregnancy and in increased loss from the body in certain fistulas. There seems to be a calcium balance between blood, bone cell and bone matrix something like the sugar balance in the liver.

All the foregoing points seem to point toward cellular activity in the calcification of bone and cartilage. Thus, six types of cells can secrete calcium to form hard structures: three epithelial cells—the ameloblast which builds enamel of the teeth, the epithelium of the mantle of the clam, and the epithelium of the bird's shell gland—and three types of connective tissue cell—the odontoblast which builds dentine in the teeth, the cartilage cell, and finally the osteoblast and bone corpuscle.

OXYGEN IN THE TREATMENT OF POSTOPERATIVE BRONCHOPNEUMONIA *

MELVIN W. BINGER, M.D.
Fellow in Medicine, The Mayo Foundation

E. STARR JUDD, M.D.

ALEXANDER B. MOORE, M.D.
AND
RUSSELL M. WILDER, M.D.
ROCHESTER, MINN.

In the symposium on treatment with oxygen in cases of pneumonia that was presented last year at the meeting of the Association of American Physicians, Binger,[1] Barach [2] and Boothby [3] suggested that the disrepute of such treatment could be accounted for by the ineffectiveness of former methods of administering the oxygen. They then described the newer apparatus, the oxygen chamber and the oxygen tent, by means of which it is possible to envelop the patient, or his head, in an atmosphere of any concentration of oxygen desired. They demonstrated that with atmospheres of about 50 per cent oxygen, anoxemia could usually be controlled, and the patient with pneumonia improved subjectively; the temperature and pulse often fell dramatically.

The present report is concerned chiefly with the treatment with oxygen in cases of postoperative pneumonia at The Mayo Clinic. Up to Jan. 1, 1927, oxygen had been used in only a few cases, but by this time a fleet of tents had been put into service, and approximately 50 per cent of the patients in whom pneumonia developed in 1927 were treated with oxygen. Therefore, if such a procedure has definite merit, it should be reflected in the mortality statistics of this year. The following data were noted:

In 1927, the pathologist named pneumonia as the cause of death in thirty-six of the postoperative cases which came to necropsy. During the preceding four years, there had been an average of forty-eight deaths, with a fluctuation, however, of from thirty-nine to fifty-six.

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* Read before the Association of American Physicians, Washington, D. C., May 1, 1928.

* From The Mayo Clinic, Rochester, Minn.

1. Binger, C. A. L.: General Considerations in Regard to Oxygen Therapy, Tr. A. Am. Phys. **42**:301, 1927.

2. Barach, A. L.: Acute Disturbance of Lung Function in Pneumonia, Tr. A. Am. Phys. **42**:303, 1927.

3. Boothby, W. M., and Haines, S. F.: Oxygen Therapy, Tr. A. Am. Phys. **42**:287, 1927.

In 1927, sixteen deaths were attributed to pneumonia in cases in which operation had been performed on the stomach or duodenum. Usually the diagnosis was made at necropsy by the pathologist; sometimes it was made by the surgeon. In the preceding year (1926), when little oxygen was used, the number of deaths from pneumonia in the corresponding group of cases was twenty-two. The deaths from all causes following operation on the stomach and duodenum fell from sixty-two in 1926, to fifty-three in 1927, a reduction of the mortality rate of 20 per cent, chiefly attributable to fewer deaths from pneumonia (table 1).

In the hospital in which most operations of the upper part of the abdomen were performed, the deaths from pneumonia diagnosed at necropsy in 1927 were twelve (in 8,124 operations) as opposed to

TABLE 1.—*Operations on the Stomach and Duodenum*

Year	Operations (Cases)	Deaths, All Causes		Deaths from Pneumonia	
		Cases	Per Cent	Cases	Per Cent of All Deaths
1926	1,393	62	4.45	22	36
1927	1,482	53	3.57	16	30

TABLE 2.—*Comparative Mortality in Two Hundred and Five Cases*

Treatment Started, Days After Operation	Cases	Deaths, All Causes		Deaths, Pneumonia Cases
		Cases	Per Cent	
1 to 4	158	19	12	4
5 or more	47	35	74	18

twenty-two (in 7,866 operations) in 1926. Oxygen had not been used in three of the twelve cases in 1927, and it had been resorted to tardily in six cases. Only three of these deaths can be attributed to failure of treatment with oxygen.

We observed 205 cases of postoperative pneumonia in which the patients were treated with oxygen. The diagnosis was confirmed in most instances by roentgenograms. If this series of cases is divided arbitrarily into those in which treatment with oxygen was started before the fifth day after operation, and those in which it was started after the fourth day, it is shown that the mortality in the latter group is six times as high as that in the former group: 74 per cent as opposed to 12 per cent (table 2). The fourth day after operation is late in many cases, since evidence of the onset of pulmonary complications can usually be detected within the first twenty-four hours after operation and the condition of the patients may be serious much earlier than the fourth day.

It is recognized that these data do not constitute biometric proof of the efficiency of treatment with oxygen. Nevertheless, in view of the fact that the treatment was given in not more than 50 per cent of all cases of postoperative pulmonary complications, that in many of these the oxygen was administered late, and that there were no other significant innovations in the treatment of patients before or after operation in 1927, we feel justified in concluding that lives have been saved.

In an endeavor to obtain other evidence of the value of the procedure, we resorted to experiments on animals. Smith [4] recently reported that he had caused aspiration pneumonia in guinea-pigs and rabbits by the intratracheal injection of infected material. Dogs are resistant to such procedures, as Cutler and Schlueter [5] have noted, but the guinea-pig proves to be surprisingly sensitive. By anesthetization with ether, exposure of the trachea by operation and intratracheal injections, we produced pneumonia almost constantly with streptococci freshly cultured from healthy throats. Furthermore, the pneumonia almost always proved fatal, most of the animals dying from extensive bronchopneumonia within two weeks. A series of such experiments was conducted. In each experiment, ten or twelve guinea-pigs were anesthetized and inoculated in an identical manner, and then half of them were subjected immediately after the operation to an atmosphere of 50 per cent oxygen and left in this atmosphere for twenty-four or forty-eight hours. The results encourage us to believe that oxygen properly administered is a life-saving measure. Sixty-six of seventy untreated guinea-pigs died within two weeks. Six of fifty-one treated guinea-pigs were killed from the second to the sixth day for examination of the lungs; twenty-two guinea-pigs died and twenty-three survived. The mortality of the treated guinea-pigs is, thus, at least 50 per cent less than that of the untreated guinea-pigs.

During the last four months, in selected cases on one of the surgical services, treatment with oxygen has been started immediately after operation and continued for from twenty-four to forty-eight hours. The patients chosen were those who had had recent colds, who were elderly or feeble, or who had been operated on in the upper part of the abdomen; in other words, they were patients concerning whom there was reason for apprehension in a consideration of postoperative pulmonary complications. Although this group was small, it is encouraging that pulmonary infection did not develop in a single instance.

4. Smith, D. T.: Experimental Aspiratory Abscess, Arch. Surg. **14**:231 (Jan.) 1927.

5. Cutler, E. C., and Schlueter, S. A.: The Experimental Production of Abscess of the Lung, Ann. Surg. **84**:256, 1926.

COMMENT

There is reason to believe that treatment with oxygen has resulted in the actual saving of life. The good results have occurred chiefly in the group of cases in which treatment was instituted reasonably early. Administration of oxygen immediately after operation and before the development of pulmonary lesion promises to be an effective method for preventing the occurrence of serious pulmonary complications.

A REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.
LOS ANGELES
E. STARR JUDD, M.D.
ROCHESTER, MINN.
LINWOOD D. KEYSER, M.D.
ROANOKE, VA.
GORDON S. FOULDS, M.D.
TORONTO
JEAN VERBRUGGE, M.D.
ANTWERP, BELGIUM
AND
ADOLPH A. KUTZMANN, M.D.
LOS ANGELES

(Concluded from page 898)

BLADDER

Tumors.—Beer,[43] at the Third Congress of the Society of International Urologists, stated that the employment of high frequency currents through the cystoscope has given excellent results in the treatment of tumors of the bladder. There are known differences in the action of the unipolar and bipolar current. The unipolar is more explosive and of a higher tension and requires greater amperage. The action of the bipolar current is more useful in producing extensive coagulation of the pedicle of a tumor. When the bladder is open, the papilloma may be held up with a clamp and the bipolar current allowed to penetrate through the tumor, which produces coagulation that extends through the pedicle in the adjacent wall of the bladder.

Beer has had excellent results in the endoscopic treatment of vesical tumors in 158 cases. In about 20 per cent of the cases, there were recurrences. Recurrences in the same site are usually due to insufficient destruction.

In the operative treatment of tumors of the bladder, Beer stated that it is necessary to prevent implantations of tumors. He suggested bringing the bladder outside the peritoneal cavity for a good exposure. The bladder should be opened with a radio knife and the various tumors coagulated and removed. Results with this treatment were satisfactory in thirty-three cases; 85 per cent of the patients were apparently cured. He has employed radium emanation planted through the cystoscope in sixteen cases with successful results in 50 per cent. The poorest results were obtained in cases of inoperable carcinoma situated in the

43. Beer, M. E.: Traitement des tumeurs de la vessie, par les agents physiques, J. d'urol. **24**:327, 1927.

region of the sphincter. In seventeen cases of carcinoma, deep roentgen-ray treatment was employed without any real cures. In certain cases, symptoms were ameliorated.

Löffler [44] reported twenty-two cases of resection of the bladder performed at the Krankenhaus in Vienna. Twenty of the operations were performed for carcinoma; one was performed for sarcocarcinoma, and one for ulcer. Most of the resections were carried out through a longitudinal suprapubic cystotomy opening under lumbar anesthesia produced with 5 per cent tropacocaine. Ureters were reimplanted in cases of ureteral involvement. The immediate mortality was 27.3 per cent, and the late mortality 14.3 per cent.

Joseph [45] stated that the intravesical treatment of malignant vesical tumors is only an emergency measure which has been frequently employed because surgical measures have been so hopeless. The so-called resection of tumors of the bladder, that is, removing part of the wall of the bladder, has in general given poor results. From a great number of cases in the literature, it has been noted that there were recurrences following operation in from 80 to 90 per cent. In many cases, the patient's life is probably shortened by resection and made worse by tenesmus, fistula formation and more rapid growth and spread of the tumor. The only exceptions are the cases in which the tumors are in the dome of the bladder, the upper aspect of the anterior wall or the upper part of the posterior aspect. Tumors in these situations are technically easier to resect. If, however, as is often the case, the tumor lies in the floor of the bladder, in the neck, or between the ureteral orifices, satisfactory resections are not technically possible. Destruction and total extirpation of the bladder cannot be considered for such cases; the patient with a small tumor will refuse this treatment for a continuance of the small amount of suffering, while the patient who has a large growth, even though consenting to the operation, has only a small chance of recovery.

The resection of a tumor of the bladder is nevertheless considered because of the occasional cure in the dome of the bladder. This is an incomplete attempt at cure and is comparable to a supravaginal amputation of the uterus in carcinoma of the body of the uterus or the enucleation of carcinoma of the breast without amputation or resection of lymphatics. Consequently, Joseph employs intravesical treatment of malignant tumors. This manner of treating vesical tumors has given,

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44. Löffler, L.: Unsere Fälle von Blasenresektion, Verhandl. d. deutsche gesellsch. f. urol., 1927, p. 361.

45. Joseph, E.: Die intravesicale Behandlung börsartiger Blasengeschwülste, Verhandl. d. deutsche gesellsch. f. urol., 1927, pp. 323 and 364.

he believes, satisfactory results. Aseptic tumors with only a few symptoms are excluded. Two methods are considered: thermocoagulation and chemicocoagulation. Joseph uses a combination of both. He covers the bleeding tumors with concentrated trichloracetic acid (chemicocoagulation), using a ureteral catheter through the cystoscope. This treatment is comparable to treatment of inoperable carcinomas of the uterus with zinc chloride. A large part of the tumor sloughs off with this treatment, the tumor becomes smaller and then becomes covered with normal mucous membrane; bleeding and oozing are practically checked. At the next treatment, the necrotic material due to the former treatment has sloughed off and trichloracetic acid is used again. In order to make this treatment more efficient, the thermocoagulation is followed by another treatment of trichloracetic acid, which gives the acid an opportunity to penetrate into the tumor.

It is understood that cure cannot be obtained from the chemicocoagulation or from the thermocoagulation and chemicocoagulation. Joseph has, however, achieved long enduring results in some cases. noting that many patients have good health and ability to work even with an inoperable tumor. He has not observed benefit from radium or deep roentgen-ray therapy and stated that in the United States the urologists are getting away from radiotherapy.

Privess [46] stated that adenomas of the bladder are not common. He reported a case in which the patient came for treatment because of hemorrhoids, but gave a history of urethral stricture, vesical distress and urinary retention. Urethral dilatation and cystoscopy revealed smooth vesical calculi and a tumor, 2.5 cm. in diameter, covered with normal mucous membrane near the neck of the bladder. Cystotomy was performed with the removal of fifty stones and extirpation of the tumor. Histologically, the tumor was similar to prostatic tissue and it was thought to be of prostatic origin. Adenomas of the bladder are benign, and become serious only by causing retention or hemorrhage. The stones were probably formed because of the obstruction to urination.

Gagucau [47] divided tumors of the bladder into four groups: (1) true papilloma, (2) papilloma with malignant degeneration, (3) carcinoma and (4) massive carcinoma.

The treatment by deep roentgen ray, while not always producing cure, sometimes causes amelioration of symptoms and regression of the size of the tumor. The combined results of radium and roentgen ray

46. Privess, M.: Ueber gutartige Geschwülste der Harnblase: Ein Fall von Cystoadenoma papillare, Trudy klinik voronežskaro universiteta, **2**:125, 1927.

47. Gagucau, M.: Des tumeurs vésicales, J. d'urol. **24**:469, 1927.

are much more satisfactory. The best results have been observed in the treatment of papillomatous tumors. Gagucau believes that surgical treatment still gives the best chance for cure, especially in cases of malignant tumor. Combination of surgical treatment with cautery and radium increases considerably the chances of success in the treatment of infiltrated carcinoma of the bladder.

Cassuto [48] reported a case of pyonephrosis resulting from obstruction to the lower part of the ureter. The patient had had urethritis for two years and occasional attacks of hematuria and pyuria. Cystoscopic examination revealed a papilloma about 3 cm. in diameter on the edge of the right ureteral orifice and closing it almost entirely. The tumor was destroyed by fulguration. One month afterward, the symptoms still continued. A right pyelogram revealed extensive pyonephrosis; drainage was instituted.

Herman [49] reported a case of neoplasm of the trigone of the bladder. The patient, a man, aged 70, gave a long history of urinary disturbance, including dysuria, difficulty and a small stream. Hematuria had been present for six months. The results of the general examination were negative. Rectal examination did not reveal enlargement of the prostate. It was impossible to pass a cystoscope because of an intravesical mass. A water-dilating cysto-urethroscope revealed a normal urethra and vesical neck, and a mass in the trigone, which was lobulated and sessile.

At operation, a lobulated tumor was found occupying practically the whole trigone, with its major portion beneath the trigone. The overlying thin mucosa was incised in the long axis and was found to be friable in the region of the anterior declivity of the tumor. Immediately beneath the mucosal covering, a multilobular, well encapsulated, yellowish-white mass was exposed. This consisted of a number of individual lobules loosely bound together but well encapsulated as a whole. The gross appearance of the tumor was characteristic in miniature of hypertrophic prostatic tissue. The mass was about 3.75 cm. in the anteroposterior diameter, and 2.5 cm. slightly below the level of the trigone in its greatest width from side to side. Approximately 1.75 cm. of the mass projected above the trigone; the remaining 2 cm. was buried within and below the trigonal musculature. The main portion of the mass, comprising about two thirds of the growth, was deeply placed and well encapsulated so that it could be shelled out with surprising ease. There was considerable bleeding from the right anterior

48. Cassuto, A.: Uro-pyonéphrose du à un papillome implanté sur le méat uretéral, Lyon. chir. **24**:253, 1927.

49. Herman, Leon: Neoplasm of the Trigone Vesicae: a Probable Instance of Hypertrophic Changes in Aberrant Prostatic Tissue, J. Urol. **19**:291, 1928.

segment of the bed of the tumor. This was controlled by packing and sutures, the latter being so placed that the interureteric bar was drawn forward to the trigonal mucosa. As the latter was necrotic and the underlying muscles atrophic, it was with some difficulty that the sutures were made to hold. The bed, on exploration bimanually, was found to be extensive, situated well above the prostate gland and sphincteric area, and to extend backward to the rectal wall, separated from the latter only by the capsule of the tumor.

The bladder was closed with drainage. Convalescence was uneventful for thirty-one days; the wound had closed with reestablishment of normal voiding. After the patient had been up for a week, he suddenly became stuporous and died in uremic coma within a period of twelve hours. The pathologic report on the tissue removed was "benign hypertrophy of the prostate gland."

There would not seem to be any question of the identity of the tumor, although certain vesical tumors classified as adenomas resemble in minute structure benign prostatic hypertrophy. The neoplasm apparently originated within or beneath the trigonal structures, and in its fully developed state was situated above the prostate gland, and at a considerable distance from the internal sphincter muscle. The normally situated prostate gland was not enlarged, and the position of the tumor and of the cavity from whence it came justified the conclusion that the tumor and the prostate gland were entirely unrelated anatomically. The question seemed to resolve itself into a differentiation of tumor originating from glandular tissue other than that comprising the prostate gland, of accessory glands in the region of the vesical outlet, and of benign hypertrophic changes in aberrant prostatic tissue.

Comparison with the growth and development of tumors known to have originated in the trigonal mucosal glands justified the conclusion that this tumor did not originate in these structures, but, in all probability, in structures beneath or within the trigonal musculature. The probabilities are that the tumor presented hypertrophic changes in aberrant prostatic tubules.

Deming [50] noted in the literature the reports of nine cases of primary carcinoma developing in diverticula of the bladder and reported one case of his own.

The age incidence in carcinoma and diverticula was between 57 and 70 years, most of the patients being close to the age of 62. All patients were men. All but one of the diverticula were infected. The diverticula were single; five were on the left side near the left ureteral orifice,

50. Deming, C. L.: Primary Carcinoma of Diverticulum of the Bladder, J. Urol. **18**:73, 1927.

four near the right ureteral orifice, and one in the median line just behind the interureteric ligament. The size of the diverticula varied from 2.5 cm. in diameter to that of a normal bladder. The vesical walls were much thickened and hypertrophied. Marked inflammation of the mucosa of the bladder was present as a result of severe infection. The urine was foul and contained a large amount of mucus. The symptoms were dysuria and obstruction extending over periods of from four months to three years. Interval hematuria was the outstanding clinical feature. Frequency was present in all cases, and is probably accounted for by the infection and inflammation of the bladder. Retention occurred in several of the cases.

The diagnosis of this condition is impossible without cystoscopy. The symptoms do not distinguish it from prostatic obstruction and carcinoma of the bladder itself. A cystogram helps to make a diagnosis of diverticulum, but not of the indwelling tumor. The cystoscope may not even disclose the tumor unless it protrudes from the mouth of the diverticulum. Furthermore, the mouths of diverticula have peculiar sphincteric actions, so that unless the stoma of the diverticulum is observed at varying intervals or at different stages of the filling and emptying of the bladder, the condition might be easily overlooked.

The treatment has been for the most part an attempt at removal of the diverticulum. Targett gave the data from the necropsy in three of the ten cases here reported. In three cases reported by Judd and Scholl the diverticulum was excised, but in the fourth case the diverticulum was so adherent that excision was not attempted. Harris reported a case in which cystotomy was performed, but the extent of the growth prohibited resection. In Deming's case, resection was readily accomplished. Young reported the only cure in a case of a small diverticulum 2 cm. in width. The carcinoma was not infiltrating and had not metastasized at the time of operation.

Death occurred from twenty-five days to two years after operative procedures. According to Targett's report on three necropsies, infection, pyelonephritis and uremia were the immediate causes of death. Metastasis was noted in one of the cases reported by Judd and Scholl in the lymph nodes along the right internal iliac vessels, and in another case, there was a recurrence in the suprapubic wound after five months. In Deming's case, signs of local recurrence appeared between the bladder and the rectum eight weeks after excision; nodules in the liver were also found which were thought to be an extension of the process.

The carcinoma in Targett's case was epithelioma. In other cases, the growth was of a papillary nature. Microscopically, the section from Deming's case showed a tumor of a high degree of malignancy; the cells were angulated, reticular and contained many mitotic figures.

Malacoplakia.—Berg [51] reported a case of malacoplakia of the bladder which had been under treatment since 1907, at which time the patient had passed two stones 0.3 cm. in diameter. The diagnosis was made by cystoscopic examination. The patient returned eighteen years later with calculous pyonephrosis on the right side. Nephrectomy was followed by uneventful convalescence. Cystoscopy three months later revealed the same picture in the bladder as had been noted eighteen years previously, except that the areas were slightly smaller and better defined. Berg believed that the process resulted from irritation due to the stones. The plaques themselves did not cause symptoms.

[ED. NOTE.—Several reports on malacoplakia of the bladder have appeared recently. Certain writers have suggested that they are a precancerous condition, others that they cause many vague symptoms. This report of Berg is interesting in that it suggests that malacoplakia may be an entirely innocuous condition.]

Grieg [52] reported a case of a multipara, aged 30, with a suprapubic tumor which had grown large over a period of eight months. It was smooth, oval and painless, was not freely movable, and did not fluctuate. It lay between the umbilicus and symphysis. Pain in the loin, radiating to the thigh was present. With the assumption that a uterine or ovarian tumor was present, laparotomy was undertaken. The tumor was extraperitoneal and easily isolated. There was no connection with the umbilicus, although there was a connection between its lower pole and the bladder. The patient was living and well seven years after removal of the tumor. Microscopically, the tumor was found to be a spindle cell sarcoma.

Twenty malignant tumors of the urachus were also noted; eight deaths followed surgical removal. Twelve of the twenty tumors were carcinomas and eight were sarcomas.

Contracture of the Neck of the Bladder.—Knorr [53] reported two cases of sclerosis and four of contracture of the neck of the bladder in women. The former ran a chronic course, resulting finally in repeated attacks of urinary retention. In both of these cases there had been a previous inflammatory condition of the neck and the trigone of the bladder, in one case due to staphylococcus and in the other to the colon bacillus. In the cases of contracture, which is a condition of muscular cramp, cystitis of the neck and trigone was also an etiologic factor.

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51. Berg, G.: Zur Malakoplakia vesicae, Verhandl. d. deutsch. gesellsch. f. urol., 1927, p. 306.

52. Grieg, D. M.: Report of a Case of Sarcoma of the Urachus, Edinburgh Med. J. **34**:425, 1927.

53. Knorr, R.: Ueber Kontraktur und Sklerose des Blasenhalses beim Weibe, Zentralbl. f. Gynäk. **51**:1154, 1927.

Slow and cautious dilatation of the sphincter is the suitable treatment in most cases.

Frühwald [54] found in a series of 1,300 endoscopies 372 cases of lesions at the neck of the bladder due to infection. Most of the patients were women. Specific urethritis was present in 42 per cent of the cases. The type of changes are: (1) in from four to six weeks following infection small nodules with circumscribed edema can be seen; these may disappear spontaneously; (2) in three months small filiform and transparent efflorescences appear, and (3) in four months polyps of varous sizes, shape and form (finger-like, club-like, cock's comb-like, forked, and cauliflower-like) appear. These polyps are occasionally the underlying cause of resistant gonorrhea; they are found even though the gonococcus is not present, and they may be the cause of persistent infection after apparent cure. These changes could only be found in 4 of 171 control cases in which there had never been any sign of gonorrheal infection. Etiologically, gonorrhea plays the chief, but not the only part. Histologic examination shows that possibly these polyps are developed from preformed epithelial nests which multiply by irritation, usually the result of gonorrhea.

Lesions of the Nerves.—McCrea [55] concluded that the vesical symptoms of tabes are of two chief clinical types: the incontinent, in which there is a definite cutting off of sensation from the higher centers, and the paretic, in which the sensory loss, although present, is not so apparent, being concealed by the interference with reflex function of the viscus. A third type exists in which the symptoms are mixed, but this type is rare. In the paretic bladder, the more prominent symptoms are due to interference with the reflex function of the organ, and are largely the result of lesions of the afferent fibers running in the autonomic pelvic nerves. In the incontinent bladder, the most obvious symptoms are similar to those of a lesion of the sensory pathway in the cord, and this sensory loss is significant in the production of muscle senses which are transmitted by the pudic nerves.

McCrea suggested that tabes may rarely affect the autonomic or visceral nerves and the somatic sensory nerves simultaneously, and if it does, never to the same degree. This explains the difference between the pelvis and pudic nerves. The most obvious cases of tabes are those presenting destruction of somatic sensory fibers, but not visceral crises.

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54. Frühwald: Veränderungen am Orificium internum urethrae bei Gonorrhoe der Frau, Dermat. Wchnschr. **84**:376, 1927.

55. McCrea, E. D.: Bladder in Tabes, Irish J. M. Sc., 1927, p. 658.

Fistula.—Roeder [56] pointed out that the interference with the blood supply of the lower part of the ureter and bladder following total hysterectomy, as a cause of postoperative ureteral and vesical fistula, deserves more consideration than it has received in the past.

The blood supply of the inner portion of the anterior vaginal wall and the apposed bladder comes from branches which originate from the inferior vesical and uterine arteries. The uterine arteries send branches to surround the vault of the vagina, the anterior branches uniting to form a single vessel which runs forward in the median line of the anterior vaginal wall. This is the arteria azygos vaginae. Large fistulas may result from blocking of these vessels in the performance of total hysterectomy.

In two patients treated by Roeder, so much bladder tissue was destroyed that it would have been impossible to approximate the edges even after extensive dissection. Roeder, therefore, made an incision in the vaginal walls through their entire thickness, starting 2.5 cm. or more from the fistula. Thick flaps were turned back to afford an ample supply of blood. These flaps of vaginal wall were dissected up to within 0.8 cm. of the margin of the fistula. The flaps were then united by several layers of chromic catgut sutures, the first suture being pulled through the wound of a previously performed suprapubic cystostomy and kept under slight tension to assist in coaptation of the vaginal flaps. The bladder was left open for drainage and a self-retaining catheter placed in the urethra. In the area remaining after the vaginal flaps had been turned into the bladder, a drainage tube was placed and brought to the surface paravaginally. This was done to prevent possible leakage of urine through the vagina and the reestablishment of the fistula.

The postoperative care involved irrigation of the urethral catheter twice daily; the irrigation was allowed to come through the suprapubic tube or wound. The drain inserted paravaginally was left in for about ten days. Results from the operation were satisfactory in both of Roeder's cases, although one of the patients died twelve days afterward from chronic nephritis and hepatitis. Necropsy showed that the bladder was firmly united at the site of repair.

Young [57] stated that the vaginal approach in operating on vesicovaginal fistulas is not always satisfactory. He reported the case of a woman, aged 31, whose bladder was accidentally opened during the removal of a hydatid mole. Eleven operations over a period of three

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56. Roeder, C. A.: A Technique for the Repair of Large Vesicovaginal Fistulae, Surg. Gynec. Obst. **45**:102, 1927.

57. Young, H. H.: Repair of Vesicovaginal Fistula: Presentation of New Instrument, Surg. Gynec. Obst. **45**:226, 1927.

years had been undertaken elsewhere in an attempt to close the fistula, but in each instance the wound had broken down and the fistula persisted. The patient's health was good and renal impairment was not demonstrable.

On examination, the uterus appeared to be normal. Slightly to the right of the median line on the anterior wall of the vagina was an area of induration with a slight depression in the center. On cystoscopy, about 20 cc. of clear urine was evacuated. The capacity of the bladder on forced distention was about 300 cc. The trigone was much distorted. Running forward and outward from the right side of the trigone was a peculiar band of tissue which was entirely separated from the wall of the bladder, except at its upper and lower ends; this bridge was entirely covered with mucous membrane. Beneath the band was the opening of the vesicovaginal fistula. The fistula could be seen from either the inner or the outer side of the bridge which spanned its orifice. The ureteral orifices could not be made out, but it was believed that the right orifice was near the fistula, and it did not seem wise to close the fistula by the vaginal route.

Suprapubic operation was carried out; the bladder was opened extraperitoneally in the median line and the orifice of the small vesicovaginal fistula was disclosed. The muscular bridge was excised. A small hook was made on the end of a large safety-pin. This was pushed through the fistula and then drawn outward. One side of the fistulous tract was impaled on the pin and drawn upward. The fistulous tract was then completely excised by a circular incision under vision. The large opening between the bladder and vagina was closed by means of purse string sutures placed through the bladder. The first layer was through the submucosa of the vagina and did not penetrate through the mucosa. This suture was of heavy chromic catgut and was tied through the bladder, thus securing complete closure of the vaginal opening. The next suture was of plain catgut treated with mercurochrome-220 soluble and approximated the musculature of the bladder; this left an irregular defect in the mucosa which was closed in a linear direction by means of a through-and-through plain catgut suture tied intravensically. The insertion of these sutures, it is to be emphasized, was facilitated by the introduction of the index finger in the vagina to elevate the site of the fistula. The bladder was closed around a large Pezzer catheter.

During the earlier days of convalescence, the patient lay on the abdomen, face downward, as suggested by Chute. Young considered this an important detail. On the tenth day she was allowed to lie on her back, but the suprapubic catheter was kept in place for three

weeks. Complete recovery with healing of the fistula and good function of the bladder resulted.

Young described several instruments for thus impaling the fistulous tract and elevating it under the operator's view so that it may be carefully dissected out. A thin tractor with two spreading blades, similar to Young's prostatectomy tractor, but with delicate nonfenestrated blades, is suggested as a suitable instrument.

[ED. NOTE.—Vesicovaginal fistula is usually attacked from below through the vagina, possibly because of the success which first attended the operation of Sims. It is interesting to note that both Roeder and Young have recently reported operations by the transvesical route. Certainly the expedient appears favorable to those who have failed with this stubbornly recurrent condition. The surgical principles of removing the mucous membrane in such a way as to prevent its regrowth between the vagina and bladder is well established. Eversion of the mucosa of the vagina into the vagina away from the bladder and invasion of the mucosa of the bladder into the bladder away from the vagina in the process of closing the defect have been emphasized in contemporary literature. The transvesical approach, together with dependent drainage of the bladder during convalescence, seems theoretically to be satisfactory. The experience of Roeder and Young seems to show that their methods are practical.

Tuberculosis.—Ormond reported a case of severe tuberculosis of the bladder which failed to improve following right nephrectomy. The remaining kidney was almost totally without function. Inguinal ureterostomy relieved the patient greatly, and function in the remaining kidney was partially restored. Treatment consisted of local, general and medication for local effect. Numerous drugs have been recommended to be taken by mouth, such as methylene-blue, guaiacol in 5 mm. capsules, belladonna, hyoscyamus and oil of sandalwood. Heliotherapy, the use of tuberculin, general nutritional methods and drugs administered hypodermically are also recommended. Local treatment has varied greatly. Because irrigations are painful, instillations have been advocated. The following drugs have been used: mercuric chloride 1:5,000 to 1:1,000; iodoform in liquid petrolatum; 5 per cent guaiacol with iodoform in petrolatum; gomenol, from 10 to 20 per cent in oil; from 0.5 to 1 per cent picric acid; 5 per cent phenol; 1 per cent mercurochrome; 5 per cent silver nitrate; methylene-blue; iodine vapor and sterile air. Excision or fulguration of the ulcer is sometimes advised.

Four types of distressing intractable cases are cited in which further radical treatment is necessary: (1) bilateral renal tuberculosis;

(2) tuberculosis of the remaining kidney, the other kidney having been removed for tuberculosis; (3) failure of the bladder to clear up following nephrectomy even though the remaining kidney is healthy, with the ureteral orifice becoming strictured and hydronephrosis resulting, and (4) advanced genital tuberculosis in the male. For treatment, the following methods have been brought forth: (1) complete excision of the bladder with implantation of the ureter into the intestine; (2) simple implantation of the ureter into the intestine; (3) implantation of the ureter to the skin of the groin, iliac or inguinal ureterostomy; (4) nephrostomy; (5) lumbar ureterostomy; (6) suprapubic cystotomy; (7) vaginal cystostomy, and (8) denervation of the bladder.]

Ormond [58] expressed the opinion that inguinal ureterostomy is the method of choice in most cases. It is easily performed, is short, relatively free from danger and the resulting fistula can be cared for satisfactorily.

Syphilis.—Gautier [59] reported a case of syphilis of the bladder. Several days after an injection of bismuth, frequency of urination and dysuria developed. On examination, a mass was felt above the prostate; this was situated in the median line and gave the same sensation as a vesical tumor. Cystoscopic examination revealed a large mass in the fundus of the bladder; its apex was an ulcerated crater. All signs and symptoms disappeared after extensive antisyphilitic treatment.

Gautier expressed the belief that the few preliminary injections of bismuth caused congestion of the bladder and attracted attention to that organ. He stated that cystoscopic examination should be performed in syphilitic patients who complain of any symptoms referred to the bladder.

Paralysis.—According to Boyd,[60] the dangers which come from overdistention of the bladder and their accompanying genito-urinary infections can be overcome in cases of acute paralysis of the bladder by suprapubic drainage. He stated that the objections to this procedure worth mentioning are few and that it has many advantages. The abdominal distention which so often exists and the lowered resistance of the tissues, due to paralysis of the abdominal wall, make certain precautions at operation necessary.

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58. Ormond, J. K.: Diversion of the Urine in Intractable and Incurable Vesical Tuberculosis, J. Urol. **19**:109, 1928.

59. Gautier, M.: Gomme syphilitique de la vessie, Presse méd. **2**:55, 1928.

60. Boyd, M. L.: Suprapubic Cystotomy in Bladder Paralysis, J. Urol. **18**: 413, 1927.

Foreign Bodies.—Wolff [61] reported two cases of foreign bodies in the bladder; in a young girl, a hairpin was found, and in a middle-aged man a piece of chewing tobacco.

The diagnosis of foreign bodies can usually be made from the history. The symptoms are usually those of cystitis. Cystoscopically, besides foreign body, the mucous membrane of the bladder is diffusely red and the blood vessels are infected.

Treatment may be either conservative or radical, depending on the circumstances.

PROSTATE

Hypertrophy.—Hunt [62] stated that the combined efforts of surgeon and clinician are more essential in the treatment of diseases of the prostate than of most other diseases. Serious organic disturbances are sometimes associated with prostatic obstruction, and, although the obstruction may be the first consideration, the coincident organic disease must also be considered in the care of the patient.

One of the most important coincidental conditions met is cardiovascular disease. Willius reviewed the records in 705 cases of enlarged prostate and noted cardiovascular disease in 42 per cent. Arteriosclerotic disease occurred most frequently (43 per cent). Arteriosclerosis associated with hypertension occurred in 36 per cent. In 8 per cent of the cases, angina pectoris was present. The incidence of cardiovascular disease is higher with prostatic obstruction than with many other diseases during the same decades, suggesting that coexisting cardiovascular disease is aggravated by persistent urinary retention.

The frequency of this association emphasizes the necessity for careful examination of the heart in all prostatic cases. Electrocardiographic studies are indispensable. Prostatectomy should not be performed in the presence of malignant hypertension, except under unusual circumstances. Most such patients live less than two years, and only 10 per cent live five years.

Renal complications must also be dealt with in the treatment of prostatic obstruction. The most common complications are insufficiency and infection; the latter is unquestionably a contributing factor in the production of the former. With drainage of the bladder and adequate treatment, the infection usually subsides. It often reappears after prostatectomy, especially when the preoperative treatment has been inadequate or too brief, and it may be the cause of death.

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61. Wolff, E. P.: Zur Kasuistik der Blasenfremdkörper, Ztschr. f. urol. Chir. **23**:428, 1927.

62. Hunt, V. C.: Reduction of Mortality Rate in Benign Prostatic Hypertrophy, J. Iowa State Med. Soc. **18**:86, 1928.

Experience has shown that the patient with prostatic obstruction is, as a rule, a poor subject for immediate operation. In 1925, 1,783 cases were reviewed in which suprapubic prostatectomy was performed at The Mayo Clinic between Jan. 1, 1913, and Jan. 1, 1925, with an average mortality of 5.5 per cent. The deaths occurring after prostatectomy were studied to determine the relationship between preoperative preparation and the mortality rate. It was shown that when patients, apparently in good general health and showing few, if any signs of renal injury were operated on immediately without preparation, there was a mortality rate nearly as great as in the group of patients in poor general health with marked renal insufficiency and infection, operated on only after adequate preparation. It has been three years since preoperative treatment has been instituted in all cases previous to prostatectomy at The Mayo Clinic. Before that time 37 per cent of patients, because of apparently good health and what appeared to be adequate cardiovascular renal reserve, were considered good subjects for the one-stage operation without any preliminary treatment. However, 44 per cent of the deaths after prostatectomy occurred in this group, and the mortality rate was 6.6 per cent. During the same period, 437 patients (24.6 per cent), considered the poorest subjects for operation, were treated by preliminary cystostomy and were adequately prepared before prostatectomy; the mortality rate in this group was 7.5 per cent. The remaining 38 per cent of patients, those with moderately impaired cardiovascular renal reserve, were treated by the installation of a permanent indwelling catheter until they were believed to be ready for operation. The one-stage suprapubic operation was used, and the mortality rate was 3.3 per cent.

The mortality rate is markedly influenced by the amount of preliminary treatment. During a period of one year in which preoperative treatment for a minimum of ten days was adopted in all cases, the following data were obtained: In 225 cases, there were 6 (2.3 per cent) deaths. A one-stage operation was performed in 188 cases with 4 deaths, a mortality rate of 2.1 per cent, as against a two-stage operation in 67 cases with death in 2, a mortality rate of 2.9 per cent.

Hunt stated that prostatectomy should never be performed without a period of preliminary treatment. In the majority of cases, satisfactory drainage can be obtained by a permanent indwelling urethral catheter. Vesical lesions, such as stones, diverticula and malignant tumors, associated with reduction of cardiovascular renal reserve, requiring a long period of preparation, still require cystostomy. Usually about 75 per cent of patients may be prepared by drainage through the urethral catheter.

Ether as a general anesthetic presents the greatest hazards in cases of prostatic obstruction, not in the administration, because it has a

wider margin of safety than have other general anesthetics, but in the subsequent renal depression and acute pulmonary complications. Patients at the age when prostatectomy is usually performed are susceptible to the inhalation type of pneumonia and to bronchial troubles. Gas anesthetic, when skillfully administered, is usually satisfactory. Regional anesthesia minimizes the postoperative renal depression and pulmonary complications.

The successful management of prostatic obstruction necessitates regarding it from a general medical point of view as a systemic disease, not only by the urologist and the surgeon, but by the internist. The surgical principles involved in prostatectomy are significant, but so far as mortality is concerned Hunt believed that a poor operation after thorough medical and urologic consideration and adequate preoperative preparation is better than a skilful operation without preparation.

Ponce de Leon [63] favored deep roentgen-ray treatment in prostatic hypertrophy. He believed that if the prognosis is good, prostatectomy should be performed in every case. If the prognosis is poor, roentgen-ray treatment should be used. He does not limit roentgen ray to the treatment of hypertrophy, but cited four patients with chronic retention and vesical distention who were definitely benefited. He expressed the belief that radiocystitis will not result and that the blood urea content is not increased. Patients for roentgen-ray treatments must be as suitably prepared as for operation, so as to eliminate the possibility of uremia. Deep roentgen-ray treatment increases the difficulty of later enucleation. He felt that it does not enhance the change of adenoma to carcinoma (as believed by Legueu), and if all other specimens of operative cases were carefully sectioned, the same percentage of malignant lesions as found after radiation could be demonstrated.

Ponce de Leon reported a case of a patient, aged 74, whose preoperative diagnosis was adenoma. During the first operation, a hard knot was felt in the prostate gland and biopsy revealed adenocarcinoma. For this reason, and also because of the patient's poor health, deep roentgen-ray treatment was substituted for the second stage of prostatectomy with marked improvement. The author stated that had the roentgen ray been used first it would have been blamed for the carcinomatous change.

Gamissans [64] wished to refute Legueu and Compar, who in sixty cases of prostatic hypertrophy in which radiotherapy was used found only slight early decongestion. He stated that the latter is false, since, on the contrary, radiotherapy may start with congestion and edema

63. Ponce de Leon, J.: Concepto urológico actual de la radioterapia profunda en el adenoma de la próstata (Replica), Rev. méd. de Barcelona **7**:496, 1927.

64. Gamissans, Angel: La radioterapia en el adenoma prostático, Rev. méd. de Barcelona **7**:483, 1927.

and therefore increase the difficulty which will subside after eight days and leave the patient improved. The cases indicated for radiotherapy are those of early prostatic hypertrophy with congestion, and chronic retention but without vesical distention, cases with only slight changes in the vesical neck and slight elongation of the prostatic urethra. The cases in which radiotherapy is contraindicated are those of chronic retention with vesical distention and marked changes in the neck of the bladder; these belong to the surgeon. Gamissans reported cases in which symptoms were not present for five years following treatment. He believed that radiotherapy does not increase the difficulty of enucleation any more than the duration of time in which other changes may take place. Finally, radiotherapy does not enhance the malignant degeneration of adenomas.

Thomas [65] outlined at length the various considerations that come into play in the management of prostatic lesions. The cystoscopic determination of the type of lesion, the amount of residual urine and the force with which the urine is expelled through the catheter, are all evaluated.

The estimation of the urea nitrogen of the blood and the excretion of phenolsulphonphthalein are the most commonly used tests of renal function by the majority of urologists. From 20 to 30 mg. of urea nitrogen in the blood are considered safe values, while values above 30 mg. for each 100 cc. are dangerous, if not prohibitive, for operation. Regarding the phenolsulphonphthalein output, definite values have not been determined. Thomas emphasized that an output of 10 per cent one week, 20 per cent the next, and 30 per cent the next is a better index for operative success than an output of 50 per cent one week and 35 per cent the next. An effort should be made to establish the stability of renal function. In cases with injury to the kidneys, reliance cannot be placed on a single test.

Thomas described what he has called the index of elimination. This index is computed by taking the ratio of the percentage output of the dye for the first and third cycles (twenty minutes each) of a one-hour period of major elimination. Normally, the ratio is 5:1 and the index is said to be 5. When the quantitative output for the first twenty-minute period is greater than, or at least equal to, that of the third period, retention of urea is not present and renal function is invariably demonstrated as excellent. Such cases are considered in the positive phase for operability. When the output for the first period is less than that for the third period, the index is obviously less than 1, the kidneys are injured and the patient is in the negative phase.

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65. Thomas, B. A.: Vital Factors in the Management of Prostatic Obstruction, Ann. Surg. **86**:563, 1927.

By repeated determination and observation of such indexes of elimination, Thomas believed that an accurate estimate can be made of renal function in a much better manner than that offered by the usual method of total excretion.

In considering the cardiovascular system, Thomas noted particularly the blood pressure of his patients. In cases of low tension in which the systolic blood pressure is 110 or less, the diastolic must be more than 60. When the diastolic is less than 60, the systolic must be more than 110. In cases of high tension in which the systolic pressure is 180 or more, the diastolic must be less than 100; when the diastolic pressure is more than 100, the systolic must not be more than 175. It is emphasized that this is not alone pulse pressure in its usual sense, but rather pulse pressure with systolic and diastolic limitations.

The significance of the Wassermann test, the determination of the coagulation time of the blood and of the blood sugar are given appropriate attention. Anemia is frequently found and must be overcome in preoperative treatment. The nervous system comes in for consideration with the possibility of tabes, multiple sclerosis, etc., as complicating factors. Thomas reported cases in which the functional nervous disorder, uncontrollable fear of death, was an evil operative omen. Rarely will the pulmonary or gastro-intestinal symptoms present features which contraindicate operation, but usually any such symptoms may be overcome, especially if caudal and transsacral anesthesia are used. Age in itself is never prohibitive if the patient's organs can be brought to function properly.

Thomas favored suprapubic prostatectomy when the gland is greatly enlarged or when intravesical complications such as stone, diverticula, or trigonal hypertrophy exist. When the hypertrophy is confined to one or both lateral lobes or the gland is small, fibrotic and presumably adherent, undoubtedly it should be removed by the perineal route. Again, in the group of patients who have the bar or glandular type of obstruction, some form of punch operation or excision with the electric knife is indicated. Thomas advocated, in many such cases, the removal of orificial obstruction by means of the punch or rongeur, suprapubically, as it is more effective and thorough, and there is less danger from infection and hemorrhage than by the urethral route.

As indications for primary cystotomy and secondary prostatectomy rather than the one-stage operation after catheter drainage, Thomas named: (1) marked cystitis, (2) intravesical complication such as stone, tumor, clots, and so forth, (3) epididymitis, (4) stricture and some cases of false passage of the urethra, (5) unusually small or sensitive urethra, (6) unusually obstructive or impassable prostate and (7) febrile cases or catheter cases in which urethral fever and chill develop.

For an anesthetic, much depends on the case. An absolute rule is not given. In certain cardiovascular, renal and pulmonary cases spinal, regional, or other forms of local anesthesia, unquestionably should be used. Most patients, if properly prepared, stand general anesthesia under gas or even ether well, much depending on the efficiency of the anesthetist.

Hemostasis is satisfactorily obtained with suture of the bleeding points at the time of operation. The use of the pneumatic bags of Hagner, Pilcher or Ballenger is advocated; packing of the prostatic fossa is the least desirable method.

Ligation of the vas as a preventive of epididymitis is regarded as unnecessary in most cases. Suction drainage is not used.

Postoperative care is held in equal importance with preoperative treatment. Sodium chloride and dextrose solutions, diuretics and cardiac tonics, especially digitalization, save many lives. The importance of vesical irrigations in the presence of infection and of general hygiene of the bladder in the prevention of pyelitis and pyelonephritis is emphasized. These old men should not be forced out of bed too soon. Many complications of epididymitis and a few of phlebitis and embolism will thereby be avoided.

[ED. NOTE.—While there are details with which some may disagree, Thomas has reviewed many features of handling prostatism which show experience and sound judgment. His description of the value of determining an index of elimination, his evaluation of blood pressure readings and his indications for the two-stage procedure are particularly appealing and seem worthy of practicing. It is to the credit of urology as a specialty that a low operative mortality has been achieved in what appears to be and has been the poorest sort of surgical risk. The low mortality rate has been the result of the many improvements in operative technic and the conscientious and detailed physiologic and biochemic studies during the periods preceding and following operation.]

Lowsley and Harrah [66] reported the unusual case of a man, aged 32, who had had urinary obstruction due to prostatic tumor for three months and was admitted to the hospital with complete urinary retention. Catheter drainage and preliminary care were followed by cystoscopy, which revealed enlargement of the prostate. Suprapubic cystostomy was performed at which time a piece of the tumor was removed for examination. Fourteen days later, the prostate was

66. Lowsley, O. S., and Harrah, F. W.: Enlargement of the Prostate Gland with Characteristics Resembling Hodgkin's Disease: Malignant Granuloma, Ann. Surg. **86**:556, 1927.

removed under regional anesthesia. At one point the prostate had infiltrated the prostatic capsule and malignancy was suspected. Microscopic examination of the growth showed newly formed granulomatous tissue, rich in plasma cells and containing mononuclear giant cells suggestive of the Sternberg type, and eosinophilic leukocytes. An inguinal lymph node, removed for section, showed simple chronic lymphadenitis.

The microscopic picture suggested a granuloma of the type of Hodgkin's disease and relative lymphocytosis. However, other features of Hodgkin's disease, which are carefully outlined by the authors, were wanting.

The unusual condition of complete urinary retention due to solid prostatic tumor in a patient, aged 32, is emphasized; a case of the kind had not been reported previously. The gradual onset of symptoms exhibited by the patient is similar to those described in most cases of adenomatous enlargements of the prostate in old men. The usual and frequent painful urination culminated in complete retention of urine rather more rapidly than in most cases of adenoma.

[Ed. Note.—The histologic picture presented is even more uncommon than the rarity of prostatic obstruction in early adult life. Sarcoma of the prostate occurs much earlier and cancerous neoplasm much later than the age of 32. Furthermore, Hodgkin's disease rarely affects the prostate. Tuberculosis, a condition at times confused with Hodgkin's lymphadenosis, was considered but none of the features of tuberculosis was present. Unfortunately, the follow-up record of the patient is not mentioned. This might reveal further interesting information in this most rare clinical and pathologic picture.]

Legueu [67] reported a number of cases of hypertrophy of the vesical neck. The hypertrophy involved not only the fibromuscular and glandular tissue, but also all the other tissues which comprise the vesical neck. Usually symptoms of retention are present over a long period. Legueu considered the glandular hypertrophy as a mild type of prostatic disease. In prostatic disease various types of adenoma may be found. There may be adenomas which weigh only a few grams, some that are barely perceptible to the eye and others so small that only the microscope can establish their existence. Functional symptoms are more marked and appear earlier in fibromuscular hypertrophy than in glandular hypertrophy. At times these hypertrophied areas contain histologic signs of secondary infection. Excision of the neck of the bladder is the best treatment for this condition.

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67. Legueu: L'hypertrophie du col vésical, Bull. Soc. franç. d'urol. **6**:222, 1927.

Kreutzmann [68] noted that although hydro-ureter and hydronephrosis have long been associated with obstructive urethral lesions the mechanism of formation of the dilatations is still an open question. His investigations have demonstrated that ureteral reflux is not common in obstructive lesions of the vesical neck and urethra. Reflux usually is unilateral and dilatation of the ureter and renal pelvis has even been demonstrated on the intact side.

Kreutzmann expressed the opinion that his investigations tend to substantiate Tandler and Zuckerhandl's theory that the dilatation of the upper part of the urinary tract is due to the vas deferens. Kreutzmann concluded that (1) in cases of hypertrophied prostates, hydro-ureter and hydronephrosis may occasionally occur as a result of the kinking of the ureters by the vas deferens; (2) the most common cause of dilatation of the upper part of the urinary tract in obstructive lesions of the vesical neck and urethra in adults is constriction of the intramural portion of the ureter; (3) this constriction is due to hypertrophy of the musculature of the bladder surrounding the ureters; (4) reflux is not common in these conditions, and when present, it is caused by an infection in the ureter resulting in a stiffening of its intramural portion, and (5) reflux is a terminal and not a primary phenomenon of prostatic hypertrophy and urethral stricture.

Alyea [69] pointed out the high incidence of epididymitis in cases of prostatic obstruction. This incidence is reported by White of London as 82 per cent, which is an unusually high percentage as White included many cases of slight induration as true epididymitis. From other reports, it would appear that about 40 per cent is a correct estimate of the occurrence of this complication.

Alyea pointed out the practical importance of preventing both preoperative and postoperative epididymitis in cases of prostatic obstruction. Statistics from various clinics emphasize the far too frequent occurrence of this complication. The advance in methods for its prevention was traced through seminal vesiculectomy, ligation of the ejaculatory ducts, to ligation of the vas in the scrotum by a closed method. It is demonstrated that the time for ligating is not at the operating table after the patient has already been handicapped by present or latent epididymitis, but at the time of his admission to the hospital, before urethral instrumentation or the insertion of a retention catheter. This is strongly advised for adoption as a ward routine in all cases of prostatic obstruction. To make this practicable, he has

68. Kreutzmann, H. A. R.: The Cause of Renal Back-Pressure in Obstructive Lesions of the Urethra and Bladder Neck, J. Urol. **19**:199, 1928.

69. Alyea, E. P.: Vaso-Ligation a Preventive of Epididymitis Before and After Prostatectomy, J. Urol. **19**:65, 1928.

described in detail the technic of vasoligation through the skin, without an anesthetic, which is done in bed or in the ward treatment room. At the Brady Urologic Institute, the vas has been ligated in fifty cases of prostatectomy according to the procedure, and the percentage of occurrence of epididymitis is four. They believe, therefore, that if this regimen is adhered to rigidly the occurrence of preoperative as well as postoperative epididymitis in the treatment of prostatic obstruction can be practically eliminated.

[ED. NOTE.—Many urologists are now employing some type of vasoligation as a routine. If done early enough, this simple procedure usually prevents epididymitis and in some cases it may save life.]

Scott [70] reviewed the dangers of rapidly emptying the chronically overdistended bladder and the various methods of decompressing such bladders more slowly. According to his observations, the best results are obtained by taking a relatively short time to empty the bladder, namely, about twenty-four hours. To accomplish this, he has successfully used an ordinary olive-tipped ureteral catheter. Decompression by means of a ureteral catheter has been used only as an emergency measure in his clinic. It has been of special value in those cases of carcinoma of the prostate in which the lumen of the prostatic urethra was so markedly decreased in size that it was impossible to pass anything larger than a filiform. In such cases the ureteral catheter also acts as a dilator, and it is possible, by inserting larger catheters every two days, to dilate the urethra rapidly so that a soft rubber catheter can be passed within a short time. The method also proved to be satisfactory in the case of a small boy having acute paradoxic incontinence due to the presence of a congenital urethral valve.

Because of the satisfactory results obtained by the apparatus now in use for decompressing the bladder in the presence of retention due to simple benign prostatic hypertrophy, the ureteral catheter has not been used in such cases. However, there does not seem to be any good reason why this method could not be used if decompression of the bladder is otherwise impossible.

Tuberculosis.—Bothe,[71] in searching the literature, found only nine cases of tuberculosis of the prostate gland without demonstrable coincident tuberculosis elsewhere in the genito-urinary tract, and to these he added a tenth case. In four of the cases, the prostate had undergone hypertrophy. His case presented the usual signs and symptoms of benign adenomatous hypertrophy of the prostate. Pros-

70. Scott, W. W.: Gradual Decompression of the Bladder with a Ureteral Catheter, J. Urol. **19**:81, 1928.

71. Bothe, A. E.: Primary Tuberculosis of the Prostate, J. Urol. **18**:494, 1927.

tatectomy was performed. On microscopic examination of the removed gland, a tuberculous focus was found. Other evidence of tuberculosis was not found. Tuberculosis of the genito-urinary tract forms about 5 per cent of all tuberculous cases found at necropsy and evidence of pulmonary tuberculosis is frequently found associated with genito-urinary tuberculosis. The prostate is frequently the seat of an associated tuberculous lesion when the other genito-urinary organs are primarily infected, but tuberculosis of the prostate, as a primary lesion in genito-urinary tuberculosis, is exceedingly rare. Hypertrophy may follow a tuberculous lesion of this gland.

[ED. NOTE.—Primary tuberculosis of the prostate is a rare condition. Grossly, it sometimes resembles carcinoma, particularly after the specimen has been removed, hardened and sectioned. Clinically, other symptoms of urinary infection usually distinguish this condition from malignancy. With secondary tuberculosis, the prostate usually becomes hard, small, fibrous and slightly nodular.]

Prostatic Secretion.—McCarthy [72] and his associates reported data regarding the chemical composition of the prostaticovesical secretions of normal young men. These secretions contain an unusually high concentration of calcium, inorganic phosphorus, "hydrolyzable" phosphorus and amino nitrogen. It is believed that the amino nitrogen and hydrolyzable phosphorus may be partly in the form of spermin.

The sugar concentration showed marked variations. The sugar content of fresh semen greatly exceeded that of blood. Glycolysis was observed during incubation of the semen at 38 C. for from nine to twelve hours. The decrease in sugar was accompanied by a rise in lactic acid. However, the amount of lactic acid formed does not account for all of the sugar lost. It is probable that glycolysis is a phenomenon attributable to living spermatozoa, and that the lactic acid is an intermediate product in the utilization of sugar.

A study of the hydrogen-ion concentration of the semen during glycolysis demonstrated an efficient buffer mechanism in this fluid.

TESTIS AND EPIDIDYMIS

Tumors of Testis.—Morris [73] gave a general discussion of the present status of the theories and classification of testicular tumor. Ewing stated that all tumors are teratomas; Chevassu maintained that there are two classes of testicular neoplasms differing essentially in cell mor-

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72. McCarthy, J. F.; Stepita, C. T.; Johnston, M. B., and Killian, J. A.: Biochemical Studies of Prostato-Vesicular Secretions, J. Urol. **19**:43, 1928.

73. Morris, J. H.: Malignant Tumors of the Testicle with Special Reference to Classification, Arch. Surg. **15**:530 (Oct.) 1927.

phology and histogenesis: (1) embryonal, distinguished by their heterologous, atypical structure and embryonal origin, and (2) the simple, homologous, unicellular growths arising from fully differentiated adult tissues. Because of the controversial nature of the field, a case was reported which was of especial interest since embryonal adenocarcinoma and seminomatous tissue were found coexisting. Morris, therefore, concluded that: (1) the large cell tumor of the testis is of the embryonal type, (2) the theory of invariable unicellular or homologous nature is herein disproved and (3) the evidence adduced from this case substantiates Ewing's theory of teratomatous origin.

[ED. NOTE.—The evidence is slowly gathering in favor of Ewing's theory of the teratomatous origin of malignant testicular tumors. Universal acceptance of this theory would tend to end the confusion which characterizes the classification. Although the classification of testicular tumors has been greatly simplified through the classic investigations of Wilms, Ewing and others, two opposing schools have arisen, one maintaining that "for practical purposes there exists only tumor of the testis, namely, a teratoma" (Ewing, O'Crowley and Martland, Wilms, Pick, Ribbert) and the other, that besides the teratomatous group, there is a large proportion of testicular neoplasms which are purely homologous or single cell tumors (seminomas) derived from the cells of the spermatic tubules (Chevassu, Frank, Schultz and Eisendrath, Sakaguchi, Vecchi, Geist and Thalheimer, Hardonia and Patel). The recording of such reports as those of Morris and Hinman, Gibson and Kutzmann will in time effect a reconciliation of these opposing schools and eradicate much of the confusion in their classifications. The teratoma of the testis is a tumor of tridermal origin, and the unicellular type of tumor, such as the seminoma, can be considered an overdevelopment of one tissue in a tridermal growth. Hence the term "teratoma testis" should be used inclusively, and, as such, signify all types of degeneration. It is well to remember that in general the malignant elements in mixed tumors are almost uniformly epithelial and therefore carcinomatous in nature, and that these carcinomatous elements in the teratoma are generally amenable to classification into one or more of three groups: (1) trophoblastic (chorio-epithelioma), (2) hypoblastic (adenomatous type), and (3) epiblastic (solid alveoli of basal cell type and tumors of the neurocytoma group)].

Proust [74] reported two cases of seminomatous tumors of the testicle observed by Proust and Mallet in 1922, in which rapid absorption was obtained with hard roentgen rays. In the first case there was a swelling

74. Proust, R.: État actuel de la radiothérapie des séminomes, Bull. de l'Assn. franç. p. l'étude du cancer **16**:247, 1927.

of the right leg, which was believed to be phlebitis, but which disappeared rapidly following radiotherapy. Since there have been similar cases, Proust assumed that the condition was due to obstruction of the lymph channels by carcinoma cells. In order to prevent the obstruction of the lymph channels and the formation of metastasis, soft rays were used which minimize roentgen-ray burns. In six cases of seminoma, the duration of life was lengthened fourteen, nineteen, thirteen and twelve months, and two patients are alive two and three years respectively since beginning treatment.

Pearlman [75] reported a case of torsion of an undescended abdominal testicle associated with malignancy. In patients, aged 18, undescended testicles are doubtless more prone to malignant change and torsion than are normally placed testes. Pearlman's case is of interest in that both conditions are seen in the one case.

Valdoni [76] stated that tumors of the genitals range as follows in the order of frequency: testis, epididymis, vas deferens, seminal vesicles and tunica vaginalis. He described a case of a small cell sarcoma of the dividing membrane of the scrotum in a boy, aged 17, which developed one and a half years after the scrotum had been injured by a hoof. Castration with complete extirpation of glands to the renal hilum was carried out. Metastasis occurred shortly afterward.

Chwalla [77] stated that sarcomas are the most common of tumors of the spermatic cord and lipomas are next in frequency. The literature, mostly French, reports about twenty-four cases. Chwalla reported a case of fibrosarcoma of the spermatic cord. The tumor was a rapidly growing spindle cell fibrosarcoma with giant cells and apparently originated either from the tunica vaginalis or the connective tissue between the cremasteric fibers.

Diagnostic Aspiration.—Huhner [78] reiterated his advocacy of aspiration of the testis as a prognostic and diagnostic procedure in sterility. He expressed the belief that operation should not be undertaken for relief of obstructive sterility without first aspirating the testis, to ascertain whether or not spermatozoa are present.

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75. Pearlman, S. J.: Malignancy in an Undescended Abdominal Testis with Torsion, J. Urol. **18**:637, 1927.

76. Valdoni, P.: Sarcoma primitivo della vaginale de testicolo, Policlinico **34**: 244, 1927.

77. Chwalla, Rudolf: Ein Fall von Fibrosarkom des Samenstranges, Ztschr. f. urol. Chir. **23**:419, 1927.

78. Huhner, Max: Aspiration of the Testicle in the Diagnosis and Prognosis of Sterility, J. Urol. **19**:31, 1928.

Hydrocele.—Campbell [79] analyzed 502 cases of hydrocele observed at the Bellevue Hospital. He pointed out that hydrocele in infants is rare, practically always congenital and associated with hernia. Ninety per cent of the patients were more than 21 years of age; 27 per cent were between 20 and 30. The right side is slightly more often affected than the left. Bilateral hydrocele was noted in four cases. The shortest duration was three days, and the longest sixty years. In more than 50 per cent of cases, the duration was between two months and three years.

Inflammation in the form of epididymitis is probably the most frequent precursor of acute or chronic hydrocele. This is most frequently gonorrheal; it may be tuberculous, and at times nonspecific. Careful examination of the exposed epididymis will in most cases reveal a pathologic organ showing the postinflammatory changes of hypertrophy or atrophy. Occasionally, hydrocele follows or accompanies orchitis. One patient had mumps immediately preceding the appearance of the hydrocele. Trauma may be and not infrequently is an etiologic factor. Thirty-four patients of this series noted an actual blow to the testis preceding onset of swelling. Campbell pointed out that operative trauma in the region of the spermatic cord, such as herniotomy entails, may cause hydrocele, and warned against undue injury to the vaginalis and testis during such procedures. Congenital hydroceles in adults are rare since the condition, if present, usually disappears spontaneously in infancy. The majority fall into the idiopathic group, but Campbell believes that unrecognized asymptomatic epididymitis is again the usual underlying process.

Pathologically, the fluid of uninfected hydroceles resembles blood serum, has a specific gravity of 1.020 to 1.026, and contains fibrin, albumin, paraglobulin, and at times cholesterin and phosphatic calculi. Microscopically, endothelial cells, cholesterin crystals, leukocytes, often spermatozoa, bacteria in infected cases, and in the event of hemorrhage, erythrocytes are shown. Caforio is quoted as stating that in view of the lower specific gravity and smaller serum content of transudates, fluid in the hydrocele is an exudate of inflammatory origin.

Symptomatically, if hydrocele is acute and the result of inflammation of the epididymis or testis (rarely trauma), pain is likely to be severe. Pain is usually proportionate to tension, severe with rapidly forming hydrocele accompanying acute gonorrheal epididymitis, and slight or absent with hydrocele and tuberculous epididymitis. Chronic hydrocele, uncomplicated by infection, is usually without symptoms save for

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79. Campbell, M. F.: Hydrocele of the Tunica Vaginalis: Study of 502 Cases, Surg. Gynec. Obst. **45**:192, 1927.

swelling. Some patients complain of a dragging sensation in the scrotum or along the cord due to the weight of the mass.

In cases of hydrocele of the tunica vaginalis, inspection reveals a pear-shaped tumor tapering into the cord. As a rule the outline is felt to be smooth and regular and the mass elastic. Occasionally, lobulation is noted. The mass is dull to percussion, transmits light, cannot be reduced (except the congenital type), and unless complicated by hernia, does not give impulse. The cord is normal unless involved in the hydrocele. The scrotal skin may be tense and shiny over acute hydroceles and over chronic large hydroceles. Usually testitis occurs behind and below the center of the tumor; rarely is it anterior and often it cannot be localized. Although puncture and withdrawal of the fluid is the surest diagnostic procedure, it should never be used unless hernia can be ruled out absolutely.

In the differential diagnosis, hernia, spermatocele, hematocele, chylocele, gumma, edema of chronic passive congestion and testicular neoplasm are considered.

Tapping or the use of a local irritant, such as painting the overlying skin with tincture of iodine, frequently accomplishes cure in infants; sometimes cure is spontaneous. In adults, spontaneous cure is never obtained. Internal medication is of no value. Tapping with or without injection and open operation are employed now in treatment. Tapping is often curative in cases of children and may be used for adults if they refuse operation and for those whose physical condition does not warrant operation. Injection of from 5 to 20 minims (0.3 to 1.25 cc.) of pure phenol after completely emptying the sac, with kneading of the scrotum to disseminate the drug to all surfaces, may be employed in uncomplicated hydroceles with thin walls and clear fluid. It should not be employed for children if it cannot be determined whether or not the sac communicates with the abdominal cavity; if it does, fluid will reform.

Open operation is the treatment of choice. Simple eversion (the bottle operation of Andrew) is useful for small hydroceles without thickened sacs. Volkmann incised the sac widely and swabbed the cavity with phenol. Convalescence is slow and the percentage of recurrences high. Campbell prefers the excision and eversion operation of Winkelman. Cutaneous and deep injections of procaine for anesthesia are made, the cord is isolated and thoroughly infiltrated, thus affording complete testicular block. By carefully incising the parietal tunica until the innermost layer presents a bluish hue, much hemorrhage may be prevented in later dissection. If the hydrocele is unusually large, most of the fluid is withdrawn before the sac is incised. With hydroceles of ordinary size, the practice is to mobilize the unopened sac by blunt

dissection along the innermost layer of tunic, infiltrating the lowest portion of the sac with anesthetic, if necessary to block the pudic nerves. The mass is then delivered through the wound and incised from end to end. The redundant tunica vaginalis is excised and complete hemostasis is obtained by a running suture in the tunica vaginalis if necessary. The remaining edges are everted and sutured behind the cord. Hemostasis is carefully watched and the testis is replaced in the scrotum. The wound is closed without drainage. A small gauze dressing and a special hemostasic bandage [80] are applied.

Complications, such as hemorrhage, infection, involvement of the testis, or recurrence of the condition, may ensue. Hematocele, if large, requires evacuation. Admonition as to the utmost care in asepsis is given. Scrotal edema may occur at times. Testicular involvement may be immediate in the form of traumatic orchitis or postoperative infection, and later there may be atrophy. In eight cases of this series, testicular involvement called for orchidectomy.

The average period in the hospital in this series was 9.3 days. Two patients died of bronchopneumonia following operations under local anesthesia.

Recurrence as quoted by Bruns was approximately 2.4 per cent. Campbell examined thirty-three cases of this series. In four a slight collection of fluid at the upper pole apart from the testis was noted. In two cases, there was definite recurrence. At the second operation it was found that two layers of the tunica vaginalis were glued together in the formation of a cyst, not involving the testicle but just above it.

[Ed. Note.—This is an excellent review of a common and much neglected lesion. As Campbell pointed out, the procedure of choice is always open operation; recurrence of the condition is three times as severe after tapping and injection. The latter methods seem somewhat obsolete but it is sometimes necessary to consider them in individual cases.]

Varicocele.—Bate [81] reviewed the literature on varicocele carefully. Petit was the first to describe varicocele as one of the symptoms of renal tumor. In 1881, Guyon and Morris gave clear accounts of cases of this condition. Bate reported fourteen cases of varicocele and renal tumor from the records of the Massachusetts General Hospital. From these he found that varicocele is a late sign and carries with it a poor prognosis. Only 28 per cent of his patients were temporarily relieved by operation. The condition is probably not often noted in early

80. For description of this unique bandage reference is made to the original article (footnote 79).

81. Bate, J.: Symptomatic Varicocele, J. Urol. **18**:649, 1927.

examinations because the patient is examined while recumbent. Thrombosis and tumor in the left renal vein occur with and without varicocele and are probably significant etiologic factors. Enlarged lymph nodes were recorded in one of the cases in which operation was performed. Pressure from the tumor would account for the varicocele in several cases.

Although many writers refer to varicocele as a symptom of lesions other than malignant tumor, the records of the Massachusetts General Hospital do not bear this out. One case was reported from the literature, in which varicocele occurred with severe pyonephrosis. Although symptomatic varicocele is a late sequel and carries with it a poor prognosis, in properly selected cases the chance for temporary relief should not be denied the patient merely because symptomatic varicocele is present. When a suddenly developing varicocele is noted in a patient of advanced age, renal tumor should be considered. Varicocele occurred in 20 per cent of the cases of hypernephroma and in 11 per cent of all malignant tumors of the kidney; it was the presenting symptom in 30 per cent of Bate's cases.

Epididymitis.—Wade,[82] in discussing treatment, divided vasoepididymitis into five stages according to clinical symptoms and pathologic manifestations.

In the first stage the patient usually presents himself complaining of pain in the groin and along the course of the vas deferens; there is a general feeling of malaise, which indicates that vasitis is present and the descending infection will soon involve the epididymis. The patient is immediately put to bed without further local treatment to the urethra or prostate, ice is applied to the painful area and 15 grains (0.972 Gm.) of calcium chloride is administered intravenously. This is repeated daily until the pain disappears. At this stage, a vas puncture with injection of the seminal vesicle on the affected side can be done satisfactorily. This is an attempt at abortive treatment.

The second stage is that in which the epididymis has become involved; there is slight swelling, tenderness and pain along the course of the vas deferens, and general malaise. Such patients also are sent to bed; calcium chloride is given daily intravenously; the scrotum is elevated and cold applications are applied. Diathermy may be used to good advantage. The epididymitis may subside at this stage or it may pass into the third stage.

In the third stage, there is considerable enlargement of the epididymis and all the symptoms are much more severe than in the previous stage. In some of these cases Wade expressed the belief

82. Wade, H. K.: Treatment of Acute Gonorrheal Epididymitis with Special Attention to Prevention of Azoospermia, J. Urol. **18**:427, 1927.

that he is justified in prescribing rest and using the expectant treatment outlined, but in many cases the Hagner operation should be performed.

In the fourth stage, the epididymis is enormously enlarged with more or less severe orchitis and hydrocele. The temperature is elevated and leukocytosis is marked. The patient is toxic and suffers intensely. In all such cases, the radical or surgical method should be carried out early.

Azoospermia can be prevented in a large percentage of cases by a carefully performed epididymotomy in selected cases.

Gurewitsch [83] discussed two cases of gonorrheal funiculitis. Clinically, the symptoms were peritoneal and suggested the diagnosis of strangulated hernia. In both cases the aponeurosis was split down to its lowermost layer to obviate any stasis, and the entire funiculus freed in layers. Closure was then carefully made, and healing occurred in eight days. Hernias did not result. According to Gurewitsch, operation hastened healing.

Urogenital Tuberculosis.—Marion [84] has performed 1,267 operations for genital tuberculosis since 1908. He has found the testis affected in about a tenth of these cases. In the remainder, the infection was localized to the epididymis.

Epididymectomy, which is more difficult to perform than nephrectomy, is possible even in advanced cases. In order to prevent the formation of fistula, Marion divides the vas and fixes it to the skin. The wound is left partly open. Cicatrization usually proceeds rapidly. He considers general postoperative treatment, such as good air, sunlight and ultraviolet lights, important. He also uses so-called antigen of Negre and Bouquet (apparently a tuberculin treatment), prepared at the Pasteur Institute. Castration is performed only as a last resort.

Wildbolz,[85] in discussing the treatment of urogenital tuberculosis, stated that he has obtained satisfactory results by epididymectomy combined with general postoperative treatment. More than 60 per cent of his patients were definitely cured, while 20 per cent died of pulmonary, renal, or other forms of tuberculosis. In order to save the testis, Wildbolz recommended early epididymectomy as the treatment of choice in cases of acute epididymitis.

Choltsoff [86] stated that tuberculosis of the prostate and vesicles usually accompanies tuberculosis of the epididymis. Isolated tuber-

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83. Gurewitsch, G. M.: Zur chirurgischen Behandlung gonorrhoischer Funikulitiden, Zentralbl. f. Chir. **54**:1225, 1927.

84. Marion: Traitement de la tuberculose génitale chez l'homme, J. d'urol. **24**: 358, 1927.

85. Wildbolz: Traitement de la tuberculose génitale chez l'homme, J. d'urol. **24**:357, 1927.

86. Choltsoff: Tuberculose uro-génitale, J. d'urol. **24**:464, 1927.

culosis of the prostate might sometimes occur, but isolated tuberculosis of the vesicles is never seen. Epididymectomy is indicated in advanced cases or in cases in which the disease is progressing rapidly. If a portion of the testis is also infected, this part should be removed. Epididymectomy and orchidectomy favorably influence prostatovesicular tuberculosis. In advanced cases, it is necessary completely or partially to remove these organs. The perineal route is usually the more desirable one.

Abricosoff [87] stated that in the majority of cases tuberculosis of the urogenital system develops from hematogenous metastasis from a primary pulmonary focus.

URETHRA

Tumors.—Wurmser [88] stated that carcinoma of the urethra is observed in the perineoscrotal, penile and balanic urethra in decreasing frequency. Two significant elements in the etiology seem to be chronic gonorrhea and the transformation of urethral polyps. Carcinoma of the glands and of the balanic urethra both develop from squamous epithelium. In the deep urethra the cells are of the cylindric type. Metastasis is common, especially to the lungs. Disturbances of micturition are usually the first symptoms; others are tumor, pain, hematuria, discharge, fistulas and adenopathy. The diagnosis and differential diagnosis are thoroughly discussed. Death in from six months to one year is the usual result in untreated cases.

[Ed. Note.—Usually carcinomas in the posterior urethra of the male, although developing on a cell that is somewhat cylindric, infrequently have squamous cell characteristics. Some of the cases reported by Wurmser were of short duration and death occurred shortly after the first appearance of trouble. In several cases reported by other observers, the appearance of the carcinoma was preceded by long periods of urinary difficulty and irritation. The tumor formation is somewhat analogous to the long standing premalignant stages preceding the development of squamous-cell tumors of the urinary bladder. Konig reported a case of urethral carcinoma developing after urinary obstruction of forty-eight years' duration, and Oberlander noted a somewhat similar case developing after forty years of urinary difficulty. Infection is unquestionably an important factor in the formation of these urethral growths. Infection usually progresses to the point of stricture and the malignant changes come later. Traumatic strictures also have the same malignant potentialities as those of infectious origin. The majority

87. Abricosoff: Tuberculose uro-génitale, J. d'urol. **24**:463, 1927.

88. Wurmser, Raymond: L'épithelioma primitif de l'urètre périnéal chez l'homme, J. d'urol. **24**:497, 1927.

of carcinomas which follow long standing infection and trauma occur in men of the cancer age and commonly occur at the usual site of stricture formation in the cavernous and membranous urethra. Occasionally they occur in the penile urethra, but rarely in the fossa navicularis. Of forty-two cases of carcinoma of the male urethra reviewed by Preiswerk, thirty-eight were in the membranous or cavernous urethra. Wurmser stated that metastatic growths are common, but it has been the experience of other observers that metastasis only occurs in the later stages. When secondary deposits occur they have the same tendency to remain localized in the primary glands as do those arising from epitheliomas of the penis. In young men, carcinoma is more likely to be papillary than squamous cell, and the long premalignant period of trauma and infection is generally absent. Papillary carcinomas in most reported cases were extremely malignant; they rapidly infiltrate the surrounding tissues and metastasize freely. Hutchison reported a case of a man, aged 22, with papillary carcinoma of the urethra; ulceration through the body of the penis occurred three weeks after the onset of swelling and obstruction. Six weeks after the first symptoms the regional glands were involved.]

Epispadias.—Sexton [89] stated that epispadias in women rarely occurs. Lower noted only forty-three cases in the literature up to 1922. He added one to the number. Sexton reported the case of a woman, aged 27, with marked separation of the labia minora and labia majora, rudimentary clitoris, an intact urethral sphincter and diastasis of the symphysis, but not associated with incontinence. Treatment was not attempted.

Priapism.—McKay and Colston [90] stated that true persistent priapism is rarely noted. Hinman had reviewed 170 cases up to 1914. They searched the literature carefully and found 22 others, making the total 192 cases. It was noted that if the erection persists for two days or more thrombosis is present in the corpora which in itself is sufficient to sustain the erection. Hence, if the underlying cause is treated successfully the erection will persist until the clot in the corpora is disposed of either by absorption or by evacuation. The immediate relief of the patient's symptoms depends on the collapsing of the penis by emptying it of this clot. It is, therefore, advocated that the erection be first relieved and the etiologic factor treated later. Various medical measures have been utilized. The use of sedatives, narcotics and hypnotics are usually of no avail. Deep anesthesia has been tried, and spinal

89. Sexton, W. G.: Epispadias in Women: Case Report, J. Urol. **18**:663, 1927.

90. McKay, R. W., and Colston, J. A. C.: Priapism: New Method of Treatment, J. Urol. **19**:121, 1928.

anesthesia in early cases. The latter should be effective provided thrombosis has not set in.

Surgical treatment is carried out as follows: (1) radical amputation if the erection is sustained by the presence of a local malignant neoplasm; (2) ligation of the dorsal arteries; (3) division of the ischiocavernosus muscles in the perineum and the arteries and nerves that pass through them, and (4) incision into the corpus cavernosum and evacuation of the contents of both sides.

McKay and Colston reported three cases with favorable results. They advocated and used the method of aspiration of the corpora, under local anesthesia. This procedure can be repeated several times if priapism returns.

McKay and Colston concluded that the easiest method of evacuating the blood clot in the corpora is by aspiration. It may be done with minimal danger. There are no contraindications to its frequent employment if necessary. The method of aspiration produces much less trauma to neurovascular mechanism producing erection than more radical surgical procedures, thereby enhancing the probability of subsequent normal erections.

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